



STIC Search Report

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**TO: Ralph J Gitomer
Location: 3d65 / 3e71
Art Unit: 1651
Wednesday, October 13, 2004**

Case Serial Number: 10/716975

**From: Noble Jarrell
Location: Biotech-Chem Library
Rem 1B71
Phone: 272-2556**

Noble.jarrell@uspto.gov

Search Notes

=> d his

(FILE 'HOME' ENTERED AT 08:18:46 ON 13 OCT 2004)

(FILE 'HCAPLUS' ENTERED AT 08:18:53 ON 13 OCT 2004

L1 1 US20040110735/PN

FILE 'REGISTRY' ENTERED AT 08:19:23 ON 13 OCT 2004

FILE 'HCAPLUS' ENTERED AT 08:19:24 ON 13 OCT 2004

L2 TRA L1 1- RN : 59 TERMS

FILE 'REGISTRY' ENTERED AT 08:19:25 ON 13 OCT 2004

L3 59 SEA L2

FILE 'WPIX' ENTERED AT 08:19:34 ON 13 OCT 2004

L4 1 US20040110735/PN

=> b hcap

FILE 'HCAPLUS' ENTERED AT 08:20:07 ON 13 OCT 2004

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FILE COVERS 1907 - 13 Oct 2004 VOL 141 ISS 16

FILE LAST UPDATED: 12 Oct 2004 (20041012/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all 11

L1 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:133428 HCAPLUS
DN 132:185416
ED Entered STN: 25 Feb 2000
TI Blood-brain barrier therapeutics
IN Ekwuribe, Nnochiri N.; Radhakrishnan, Balasingam; Price, Christopher H.;
Anderson, Wesley R., Jr.; Ausari, Aslam M.
PA Protein Delivery, Inc., USA
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 34

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000009073	A2	20000224	WO 1999-US18248	19990812
WO 2000009073	A3	20000629		
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
US 6703381	B1	20040309	US 1998-134803	19980814
CA 2340418	AA	20000224	CA 1999-2340418	19990812
AU 9956726	A1	20000306	AU 1999-56726	19990812
AU 772494	B2	20040429		

Searched by Noble Jarrell

EP 1105142	A2	20010613	EP 1999-943676	19990812
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				
IE, SI, LT, LV, FI, RO				
BR 9914280	A	20011113	BR 1999-14280	19990812
JP 2002522463	T2	20020723	JP 2000-564577	19990812
US 2004102381	A1	20040527	US 2003-716578	20031119
US 2004110735	A1	20040610	US 2003-716975	20031119 <--
PRAI US 1998-134803	A	19980814		
WO 1999-US18248	W	19990812		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
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WO 2000009073	ICM	A61K	
US 6703381	ECLA	A61K047/48H4P	
US 2004102381	ECLA	A61K047/48H4P	
US 2004110735	ECLA	A61K047/48H4P	<--

AB The present invention relates to amphiphilic drug-oligomer conjugates capable of traversing the blood-brain barrier and to methods of making and using such conjugates. Amphiphilic drug-oligomer conjugates comprise a therapeutic compound conjugated to an oligomer, wherein the oligomer comprises a lipophilic moiety coupled to a hydrophilic moiety. The conjugates of the invention further comprise therapeutic agents such as proteins, peptides, nucleosides, nucleotides, antiviral agents, antineoplastic agents, antibiotics, etc., and prodrugs, precursors, derivs. and intermediates thereof, chemical coupled to amphiphilic oligomers. One example conjugate prepared was Met-enkephalin with a succinimidyl triethylene glycol monohexadecyl ester derivative

ST blood brain barrier conjugate peptide oligomer

IT Enkephalins

RL: RCT (Reactant); RACT (Reactant or reagent)
(analog; blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT Blood-brain barrier
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT Antibodies
Blood-coagulation factors
CD4 (antigen)
Hemoglobins
Hypothalamic hormones
Interferons
Opioids
Peptides, biological studies
Proteins, general, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT 9004-10-8DP, Insulin, conjugates with polyoxyalkylene derivative, biological studies 259229-23-7DP, conjugates with peptides

RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT 57-88-5, Cholesterol, reactions 111-46-6, reactions 112-27-6, Triethylene glycol 112-82-3 623-65-4, Palmitic anhydride 4484-59-7, Triethylene glycol monohexadecyl ether 6066-82-6, Hydroxysuccinimide 13887-98-4, 3,6,9-Trioxaundecanedioic acid 58569-55-4, Met-enkephalin 74124-79-1, N,N'-Disuccinimidyl carbonate

RL: RCT (Reactant); RACT (Reactant or reagent)
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT 5274-61-3P 31255-25-1P 62304-85-2P, Triethylene glycol monohexadecanoate 259228-98-3P 259228-99-4P 259229-23-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT 4484-59-7DP, conjugates with enkephalin 5274-61-3DP, conjugates with enkephalin 62304-85-2DP, conjugates with enkephalin 259229-00-0P 259229-01-1DP, conjugates with enkephalin 259229-02-2DP, conjugates with enkephalin

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT 50-56-6, Oxytocin, biological studies 74-79-3, Arginine, biological studies 1407-47-2, Angiotensin 9000-96-8, Arginase 9001-73-4, Papain 9001-78-9 9001-99-4, Ribonuclease 9002-07-7, Trypsin 9002-60-2, Adrenocorticotrophic hormone, biological studies 9002-62-4, Prolactin, biological studies 9002-64-6, Parathyroid hormone 9002-71-5, Thyroid stimulating hormone 9002-72-6, Somatotropin 9004-07-3, Chymotrypsin

9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies
 9011-97-6, Cholecystokinin 9015-68-3, Asparaginase 9026-93-1,
 Adenosine deaminase 9038-70-4, Somatomedin 9054-89-1, Superoxide
 dismutase 11000-17-2, Vasopressin 11096-26-7, Erythropoietin
 17650-98-5, Caerulein 39379-15-2, Neurotensin 51110-01-1, Somatostatin
 52906-92-0, Motilin 60118-07-2, Endorphin 74913-18-1, Dynorphin
 80043-53-4, Gastrin-releasing peptide 82785-45-3, Neuropeptide Y
 85916-47-8, Katalcalcin (human) 139639-23-9, Tissue plasminogen activator
 259229-03-3 259229-04-4 259229-05-5 259229-06-6 259229-07-7
 259229-08-8

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (blood-brain barrier therapeutics comprising drug-oligomer conjugates)

=> b wpix

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FILE LAST UPDATED: 11 OCT 2004 <20041011/UP>
 MOST RECENT DERWENT UPDATE: 200465 <200465/DW>
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=> d all 14

L4 ANSWER 1 OF 1 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
 AN 2000-256190 [22] WPIX
 DNC C2000-078134
 TI Amphiphilic drug-oligomer conjugate for delivery of therapeutic agents,
 used to treat central nervous system disorders, or diagnostic agents
 across the blood brain barrier.
 DC A96 B04 B05
 IN ANDERSON, W R; ANSARI, A M; EKWURIBE, N N; PRICE, C H; RADHAKRISHNAN, B;
 AUSARI, A M; ANDERSON, W; RHADAKRISHNAN, B
 PA (PROT-N) PROTEIN DELIVERY INC; (NOBE-N) NOBEX CORP; (NOBE-N) NOBEX INC;
 (ANDE-I) ANDERSON W R; (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N;
 (PRIC-I) PRICE C H; (RADH-I) RADHAKRISHNAN B
 CYC 83
 PI WO 2000009073 A2 20000224 (200022)* EN 75 A61K000-00
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
 OA PT SD SE SL SZ UG ZW
 W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
 GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
 MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
 US UZ VN YU ZW
 AU 9956726 A 20000306 (200030)
 EP 1105142 A2 20010613 (200134) EN A61K031-705
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI
 BR 9914280 A 20011113 (200201) A61K031-704
 KR 2001072472 A 20010731 (200209) A61K047-48
 CN 1323213 A 20011121 (200218) A61K031-704
 JP 2002522463 W 20020723 (200263) 78 A61K047-48
 MX 2001001694 A1 20020501 (200368) A61K000-00000
 US 6703381 B1 20040309 (200418) A61K031-56
 US 2004102381 A1 20040527 (200435) A61K038-23
 US 2004110735 A1 20040610 (200438) A61K031-56 <--
 AU 772494 B2 20040429 (200457) A61K031-705

ADT WO 2000009073 A2 WO 1999-US18248 19990812; AU 9956726 A AU 1999-56726 19990812; EP 1105142 A2 EP 1999-943676 19990812, WO 1999-US18248 19990812; BR 9914280 A BR 1999-14280 19990812, WO 1999-US18248 19990812; KR 2001072472 A KR 2001-701888 20010213; CN 1323213 A CN 1999-812133 19990812; JP 2002522463 W WO 1999-US18248 19990812, JP 2000-564577 19990812; MX 2001001694 A1 WO 1999-US18248 19990812, MX 2001-1694 20010213; US 6703381 B1 US 1998-134803 19980814; US 2004102381 A1 Div ex US 1998-134803 19980814, US 2003-716578 20031119; US 2004110735 A1 Div ex US 1998-134803 19980814, US 2003-716975 20031119; AU 772494 B2 AU 1999-56726 19990812

FDT AU 9956726 A Based on WO 2000009073; EP 1105142 A2 Based on WO 2000009073; BR 9914280 A Based on WO 2000009073; JP 2002522463 W Based on WO 2000009073; MX 2001001694 A1 Based on WO 2000009073; US 2004102381 A1 Div ex US 6703381; US 2004110735 A1 Div ex US 6703381; AU 772494 B2 Previous Publ. AU 9956726, Based on WO 2000009073

PRAI US 1998-134803 19980814; US 2003-716578 20031119; US 2003-716975 20031119

IC ICM A61K000-00; A61K000-00000; A61K031-56; A61K031-704; A61K031-705; A61K038-23; A61K047-48

ICS A61K038-00; A61K038-04; A61K038-11; A61K038-21; A61K038-22; A61K038-26; A61K038-27; A61K038-33; A61K038-36; A61K038-42; A61K038-46; A61K038-48; A61K039-395; A61K045-00; A61P005-02; A61P005-10; A61P005-14; A61P005-18; A61P029-00; A61P043-00; C07K014-70; C07K017-00

AB WO 2000009073 A UPAB: 20000508
 NOVELTY - Amphiphilic drug-oligomer conjugate comprising a therapeutic compound conjugated to an oligomer comprising a lipophilic moiety coupled to a hydrophilic moiety, is new.
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
 (1) an amphiphilic oligomer-enkephalin conjugate selected from the group consisting of DHA Met-enkephalin-Lys, linoleic Met-enkephalin-Lys, cetyl Met-enkephalin-Lys, cholesterol Met-enkephalin-Lys, palmitate-teg Met-enkephalin-Lys, and di-palmitate-teg Met-enkephalin-Lys;
 (2) an amphiphilic oligomer-enkephalin conjugate where the oligomer comprises a lipophile coupled to a hydrophile by a hydrolyzable bond, the conjugate being DHA Met-enkephalin-Lys, linoleic Met-enkephalin-Lys or cetyl Met-enkephalin-Lys;
 (3) an amphiphilic oligomer-enkephalin conjugate where the oligomer comprises a lipophile coupled to a hydrophile by a non-hydrolyzable bond, the conjugate being cholesterol Met-enkephalin-Lys, palmitate-teg Met-enkephalin-Lys or di-palmitate-teg Met-enkephalin-Lys;
 (4) a method for activating a receptor comprising bringing the receptor into contact with the novel conjugate;
 (5) a method for delivering a therapeutic compound across the blood-brain barrier comprising administering the novel conjugate;
 (6) a method for inducing analgesia in a subject, comprising administering the novel conjugate; and
 (7) a method for altering the binding affinity of a peptide or protein to its receptor, comprising conjugating the peptide to the novel conjugate.
 ACTIVITY - Cerebroprotective.
 MECHANISM OF ACTION - None given.
 USE - The conjugates are capable of traversing the blood-brain barrier and so delivering therapeutic agents used in the treatment of disease states associated with the central nervous system (CNS) or for delivering diagnostic agents across the blood brain barrier.
 ADVANTAGE - The conjugates are stable in the bloodstream and resist degradation by the enzymes of the blood brain barrier and in the CNS. The conjugates readily cross the blood brain barrier.
 Dwg.0/10

FS CPI
 FA AB; DCN
 MC CPI: A12-V01; B01-D02; B04-C01B; B12-K04; B14-J01

=> b home

FILE 'HOME' ENTERED AT 08:20:26 ON 13 OCT 2004

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=> d his

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(FILE 'HOME' ENTERED AT 08:18:46 ON 13 OCT 2004)

FILE 'HCAPLUS' ENTERED AT 08:18:53 ON 13 OCT 2004
L1      1 US20040110735/PN

FILE 'REGISTRY' ENTERED AT 08:19:23 ON 13 OCT 2004

FILE 'HCAPLUS' ENTERED AT 08:19:24 ON 13 OCT 2004
L2      TRA L1 1- RN :      59 TERMS

FILE 'REGISTRY' ENTERED AT 08:19:25 ON 13 OCT 2004
L3      59 SEA L2

FILE 'WPIX' ENTERED AT 08:19:34 ON 13 OCT 2004
L4      1 US20040110735/PN

FILE 'HCAPLUS' ENTERED AT 08:31:49 ON 13 OCT 2004
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      E RECEPTORS/CT
      E DRUG/CT
      E DRUGS/CT
      E E3+ALL
      E OLIGOMER/CT
      E OLIGOSACCHARIDES/CT
      E E3+ALL
      E OLIGONUCLEOTIDES/CT
      E E3+ALL
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L7      146660 (A12-V01 OR B04-C? OR C04-C?)/MC
L8      499 L6 AND (LIOPHIL? AND HYDROPHIL?)/BIX
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      E EKWURIBE N/AU
L9      37 E3-4
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L10     10 E3
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L11     34 E3, E10
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L12     124 E3, E20
      E ANSARI A/AU
L13     25 E3, E7
L14     34 (PROTEIN AND DEIVERY OR NOBEX)/CS, PA
L15     12 L5 AND L9-13
L16     11 L15 AND L6-8
L17     3508 L5 AND L6-8
L18     1747 L5 AND (L6 OR L8) AND L7
L19     20 L18 AND L8-13
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L21     0 L20 NOT L19
L22     1727 L18 NOT L19
L23     255 L22 NOT (PY>1998 OR AY>1998 OR PRY>1998)
L24     15 L5 AND L7 AND L8
L25     15 L24 AND L8-14
L26     758 L7 AND (LIOPHIL? AND HYDROPHIL?)/BIX
L27     20 L5 AND L26
L28     16 L27 AND L8-14
L29     4 L27 NOT L28
L30     98843 (B04-K? OR C04-? OR B04-B04A6 OR C04-B04A6 OR B04-NO2? OR C04-N
L31     415 L30 AND L5
L32     6 L31 AND L8-13
L33     2 L31 AND L14
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L37     84 L36 AND L6-7
      SEL AN 5
L38     0 L36 AND (L8 OR L26)

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 L40 322 DRUGS+OLD,NT/CT (L) AMPHIPHIL?
 E MEDICINES/CT
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 E POLYPEPTIDE/CT
 E E10+ALL
 L42 953 POLYPEPTIDE#/CW
 L43 168882 OLIGOSACCHARIDES+OLD,NT/CT
 L44 57749 OLIGONUCLEOTIDES+NT/CT
 L45 35325 NUCLEOTIDES+NT/CT (L) OLIGO?
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 E E4+ALL
 E DISACCHARIDES/CT
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 L49 1 L40 AND L48
 L50 1066922 DRUGS+OLD,NT/CT
 L51 24 L50 AND L48
 L52 2 L51 AND L39
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 L53 61 E3-7
 E RADHAKRISHNAN B/AU
 L54 55 E3,E7-8
 E PICE C/AU
 E PRICE C/AU
 L55 123 E3,E10-11
 E PRICE CHRISTOPHER/AU
 L56 36 E3,E11-12
 E ANDERSON W/AU
 L57 201 E3,E48-50
 E ANDERSON WESLEY/AU
 L58 35 E3,E6-8
 E ANSARI A/AU
 L59 100 E3,E13-15
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 L60 11 E5
 L61 54 (PROT? AND DELIVERY OR NOBEX)/CS,PA
 L62 1 L51 AND L53-60
 L63 1 L51 AND L61
 L64 1 L62-63
 L65 23 L51 NOT L64
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 L69 4 L39 AND L48
 L70 0 L69 AND L53-61
 L71 4 L69 AND (PY<=1998 OR AY<=1998 OR PRY<=1998 OR PD<19980814 OR AD
 SEL AN 2-3
 L72 2 E9-12 AND L71
 L73 4 L68 OR L72

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L74 22 L19 OR L20 OR L25 OR L28 OR L32

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L75 449526 (D4.680.140.750. OR G3.880.750.)/CT
 L76 593315 D1.20.230./CT
 L77 806 L76 AND AMPHIPHIL?
 L78 627 (D1.20.700. OR D4.635. OR D4.680.685.60. OR D4.140.)/CT AND (LI
 L79 10 L75 AND L76-77 AND L78
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 L80 7 E3-4
 E RADHAKRISHNAN B/AU
 L81 10 E3
 E PRICE C/AU
 L82 190 E3,E11-12
 E ANDERSON W/AU
 L83 265 E3,E26

E ANSARI A/AU
 L84 188 E3,E10
 L85 17 (PROT? AND DELIV? OR NOBEX)/CS
 L86 0 L79 AND L80-84
 L87 0 L79 AND L85
 L88 4 L79 AND PY<=1998
 SEL AN 1
 L89 1 E1 AND L88
 L90 38 L75 AND L77
 L91 0 L90 AND L80-85
 L92 17 L90 AND PY<=1998
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 L94 28 L75 AND L78
 L95 0 L94 AND L80-85
 L96 19 L94 AND PY<=1998
 SEL AN 1-2 5-6 8 12 15
 L97 7 E4-10 AND L96
 SEL AN 1-2
 L98 2 E11-12 AND L97

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L74 ANSWER 1 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
 AN 2004-452588 [43] WPIX
 DNC C2004-169467
 TI New modified active agent derivatives with improved bioavailability
 comprising parent drug, e.g. anticancer agent, plus fluorinated
 hydrocarbon chain and recognition or hydrophilizing moiety.
 DC A96 B04 B05 C03
 IN CONTINO, P C; DURAND, G; JASSERON, S; PERINO, S; POLIDORI, A; PUCCI, B;
 CONTINO-PEPIN, C
 PA (SALL-I) SALLES J P; (UYAV-N) UNIV AVIGNON & PAYS DU VAUCLUSE; (TSPH-N) TS
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 CYC 107
 PI FR 2846969 A1 20040514 (200443)* 53 C07K002-00 <--
 WO 2004043993 A2 20040527 (200443) FR C07K002-00 <--
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 LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
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 DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP
 KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG
 PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ
 VC VN YU ZA ZM ZW
 ADT FR 2846969 A1 FR 2002-14077 20021108; WO 2004043993 A2 WO 2003-FR3336
 20031107
 PRAI FR 2002-14077 20021108
 IC ICM C07K002-00
 ICS A61K031-70; A61K031-706; A61K038-02;

AB FR A61K047-48; A61K049-00; A61P035-00; C07H003-02; G01N033-574
 2846969 A UPAB: 20040709
 NOVELTY - Modified active agent derivatives (I) containing an amino acid residue or peptide chain, a fluorinated hydrocarbon chain and a recognition or hydrophilizing moiety in addition to the parent active agent residue are new.

DETAILED DESCRIPTION - Modified active agent derivatives (I) containing an amino acid residue or peptide chain, a fluorinated hydrocarbon chain and a recognition or hydrophilizing moiety in addition to the parent active agent residue are new.

PA = active agent acting on a biological target;

x, a, b = 0 or 1;

X = peptide chain containing 1-5 amino acid residues;

AA1, AA2, AA3 = amino acids;

R = molecule recognized by the target of PA or a hydrophilic moiety for modifying the hydrophilic-lipophilic balance (HLB) value of (I);

Y1 = 4-12C fluorinated hydrocarbon chain containing a C(O), NH, OC(O)NH, S or O group allowing attachment to a terminal of the (AA3)b-(AA2)a-(AA1) chain or to the side-chain of one of the amino acids AA1-AA3;

The PA-(X)x moiety is bonded to the (AA3)b-(AA2)a-(AA1) chain via the side-chain of one of the amino acids AA1 - AA3 or to a terminal of the chain.

An INDEPENDENT CLAIM is also included for biologically active molecules containing a fragment of formula (II).

R' = monosaccharide, aminated sugar derivative, polysaccharide, polyether, polyol, peptide, natural or synthetic hormone or antibody.

ACTIVITY - Cytostatic; Antiinflammatory; Antibacterial; Analgesic; Neuroleptic; Fungicide; Antirheumatic; Antiarthritic; Antipsoriatic; Antidiabetic; Ophthalmological; Immunosuppressive; Vasotropic; Neuroprotective; Nootropic; Antiparkinsonian; Vulnerary; Dermatological.

MECHANISM OF ACTION - Antioxidant; Antiradical; Angiogenesis inhibitor.

USE - The active agent component (PA) is specifically an anticancer, anti-free radical, antiinflammatory, antiseptic, analgesic, neuroleptic or antifungal agent (all claimed). In particular various specific compounds (I) are used for treating and/or preventing cancer (e.g. where PA is Ara-C or melphalan), for detecting the presence of cancer cells (e.g. where PA comprises an Arg-Gly-Asp sequence), for treating and/or preventing disorders associated with oxidative stress and oxygenated radical species formation (e.g. where PA is N-benzylidene-tert. butylamine) or for blocking angiogenesis (e.g. where PA is thalidomide) (all claimed). Other conditions potentially treatable with (I) include rheumatoid arthritis, psoriasis, diabetic retinopathy, immunological disorders, ischemia-reperfusion syndrome, Alzheimer's disease, Parkinson's disease, lesions due to UV or ionizing radiation, melanoma and cellular aging. Cosmetic use for combating aging is also possible. The use of (II) for increasing the bioavailability of active agents is also claimed.

ADVANTAGE - (I) show improved vector/targeting properties and bioavailability compared with the parent active agents PA. They have a clearly defined structure, are easy to prepare and have controllable solubility for easy formulation.

Dwg.0/1

FS CPI

FA AB; GI; DCN

MC CPI: A12-V01; B02-Z; B04-B03A; B04-C01;
 B04-C02; B04-C03C; B04-D01; B04-G01; B04-J01;
 B06-D03; B07-D12; B10-A07; B10-A20; B10-B01A; B12-K04A1; B14-A01;
 B14-A02; B14-A04; B14-C01; B14-C03; B14-C09B; B14-F02D; B14-F05;
 B14-G01; B14-G02; B14-G03; B14-H01; B14-J01; B14-J01A3; B14-J01A4;
 B14-J02; B14-N03; B14-N17C; B14-R01; B14-S08; C02-Z; C04-B03A
 ; C04-C01; C04-C02; C04-C03C;
 C04-D01; C04-G01; C04-J01; C06-D03;
 C07-D12; C10-A07; C10-A20; C10-B01A; C12-K04A1; C14-A01; C14-A02;
 C14-A04; C14-C01; C14-C03; C14-C09B; C14-F02D; C14-F05; C14-G01;
 C14-G02; C14-G03; C14-H01; C14-J01; C14-J01A3; C14-J01A4; C14-J02;
 C14-N03; C14-N17C; C14-R01; C14-S08

L74 ANSWER 2 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2004-450218 [42] WPIX

DNC C2004-168730

TI Natriuretic compound conjugate useful in the treatment of e.g. congestive heart failure, comprises natriuretic compound and at least one modifying moiety.

DC A96 B04

IN EKWURIBE, N N; JAMES, K D; MALKAR, N B; MILLER, M A;
 RADHAKRISHNAN, B
 PA (NOBE-N) NOBEX CORP
 CYC 105
 PI WO 2004047871 A2 20040610 (200442)* EN 125 A61K047-48 <--
 RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE
 LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH
 PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN
 YU ZA ZM ZW
 ADT WO 2004047871 A2 WO 2003-US37996 20031112
 PRAI US 2002-429151P 20021126
 IC ICM A61K047-48
 AB WO2004047871 A UPAB: 20040702
 NOVELTY - A natriuretic compound comprises a natriuretic compound
 containing a natriuretic molecule NPR-A (natriuretic peptide receptor-A)
 binding site and at least one modifying moiety conjugation site, and at
 least one modifying moiety attached to the modifying moiety conjugation
 site.
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
 (a) preparation of the natriuretic compound conjugate;
 (b) modified pro-polynatriuretic peptide conjugate comprising: at
 least one natriuretic peptide unit having a modifying moiety conjugation
 site and an NPR-A binding site, at least one modifying moiety attached to
 the modifying moiety conjugation site of at least one of the natriuretic
 peptide units, a leader sequence and an enzymatically cleavable spacer
 coupling the leader spacer to a first natriuretic peptide conjugate;
 (c) natriuretic peptide analog (A) comprising an amino acid sequence
 having at least one modifying moiety conjugation site, an NPR-A binding
 region and at least one substituted Lys residue, as compared to a native
 natriuretic peptide amino acid sequence. The substituted Lys residue is
 not the amino acid modifying moiety conjugation site;
 (d) natriuretic peptide analog (B) comprising sequence
 CFGRX'1aMDRISSSSGX'2aGC;
 (e) natriuretic peptide analog (C) having sequence
 X'1b-CFGRX'3bMDRISSSSGLGC-X'2b;
 (f) natriuretic peptide analog (D) having sequence
 X'1c-CFGRX'3cMDRIGLGC-X'2c;
 (g) natriuretic peptide analog (E) having sequence
 X'1d-CFGRX'3dMDRIX4GLGC-X'2d;
 (h) natriuretic peptide analog (F) having sequence
 SPX'1eMMHX'2eSGCFGRRLDRIGSLGSLGCNVLRX'3eY3 containing a modifying moiety
 conjugated at the S site;
 (i) a natriuretic peptide analog (G) having sequence
 SPZ1MVQSGS-CFGRZ2MDRISSSSX'1fx'2fx'3fc and further comprising a
 natriuretic peptide conjugate comprising a modifying moiety conjugated to
 at least one Lys residue;
 (j) natriuretic peptide (H) having sequence
 KCFKGKNRDX'1gKX'2gQSGXLX'3gC-NSFKY and further comprising a natriuretic
 peptide conjugate comprising a modifying moiety conjugated to at least one
 Lys residue;
 (k) hBNP analog comprising a substitution selected from Lys14Arg or
 Lys14Gly; Lys27Arg or Lys27Gly; or Lys3Arg or Lys3Gly;
 (l) natriuretic compound conjugate (C2) comprising natriuretic
 compound comprising natriuretic molecule NPR-A binding site and at least
 one modifying moiety conjugation site;
 (m) compounds of formulae (m1)-(m6); and
 (n) preparation of compounds of formulae (m1)-(m6).
 X'1a = amino acid that does not comprise a conjugation site
 (preferably Arg);
 X'2a = amino acid that comprises a modifying moiety conjugation site
 (preferably Lys);
 X'1b = amino acid sequence containing 1-10 amino acids (preferably
 SPY1MVQSGS, or N-terminal tails and C-terminal segments of N-terminal
 tails of natriuretic peptides optionally comprising a substitution
 selected from Lys-to-Gly, Lys-to-Arg, Gly-to-Lys or Arg-to-Lys or an
 inserted Lys);
 X'2b = amino acid sequence containing 1-10 amino acids (preferably
 Y2VLRH, or C-terminal tails and N-terminal segments of C-terminal tails
 of natriuretic peptides optionally comprising a substitution selected from
 Lys-to-Gly, Lys-to-Arg, Gly-to-Lys or Arg-to-Lys or an inserted Lys);
 X'3b = amino acid other than Lys (preferably Arg or Gly);
 Y1 = modifying moiety conjugation site;
 Y2 = amino acid other than Lys (preferably Arg);

X'1c = peptide containing 1-9 amino acids (preferably SPY1MVQSGS, especially SPKMVQSGS);
 X'2c = peptide containing 1-6 amino acids (preferably Y2VLRRH or RVL);
 X'3c = amino acid other than Lys (preferably Arg or Gly, especially Arg);
 X'1d = amino acid sequence containing 1-10 amino acids (preferably a sequence native to the natriuretic peptide, especially SPY1MVQSGS);
 X'2d = amino acid sequence containing 1-10 amino acids (preferably a sequence native to the natriuretic peptide, especially Y2VLRRH);
 X4 = amino acid sequence containing 1-4 amino acids;
 X'3d = amino acid other than Lys (preferably Arg or Gly);
 Ca = alkyl;
 m = 1-20;
 n = 2-25;
 PAG = polyalkylene glycol moiety;
 n = 2-25;
 Xa = a linking moiety;
 Xb = O or N;
 o = 1-15;
 X'1e and X'2e = Lys, Arg or His;
 X'3e = Arg or His;
 Z1 and Z2 = Arg or an amino acid other than Lys;
 X'1f = Gly, Met, Leu, Phe, Ile or their conservative substitution;
 X'2f = Leu, Trp, Tyr, Phe or their conservative substitution;
 X'3f = Gly or Arg or their conservative substitution;
 X'1g = T, a, R, H, P, T or E;
 X'2g = K, N-methyl, Arg, S, D or P;
 X'3g = Arg, K, Y, F, S, Om, Har, para-amidinophenyl Ala, I or any other amino acid that has a positive charge other than Gly or Tyr;
 Y3 = not defined.

ACTIVITY - Cardiant; Hypotensive.

MECHANISM OF ACTION - Natriuretic peptide receptor-A (NPR-a) agonist;
 Cyclic guanosyl monophosphate (cGMP) synthesis stimulator;
 Renin-angiotensin-aldosterone system inhibitor.

USE - The conjugates are used for the treatment of a condition involving an excess level of extracellular fluid e.g. chronic or acute congestive heart failure and hypertension (claimed).

ADVANTAGE - The modified natriuretic compound conjugates exhibit increased resistance to enzymatic degradation (preferably a protease degradation) relative to the corresponding unconjugated natriuretic compound, improved stability in the presence of plasma, proteases, liver homogenate, acidic conditions and/or basic conditions, increased circulating shelf-life, increased bioavailability and/or prolonged duration of effect, retain a therapeutically significant % of cGMP stimulating activity, such as (at least 30, preferably at least 70, especially at least 90)%, improved NPR-A receptor binding activity; improved half-life circulation, have improved ability to pass through a GI tract and enter blood stream, improved solubility in aqueous environments and organic solvents, improved ability to cross cell membranes, improved ability to traverse blood brain barrier, and improved ability to target a certain receptor, cell tissue or organ, relative to the corresponding unconjugated natriuretic compound. The modified natriuretic compound conjugates are more hydrophilic, more amphiphilic and more lipophilic than the corresponding unconjugated natriuretic compound, and is non-immunogenic. The oral administration of the natriuretic peptides due inhibition of to reduced degradation, reduces the hospital costs associated with other congestive heart failure (CHF) therapies by enabling self administration, which further expands the therapeutic use of the natriuretic peptides including administrations in early stage and acute and chronic CHF. The conjugates further lack the negative effects and risk of sudden death associated with the inotropic and digitalis drugs.

Dwg.0/5

FS CPI

FA AB; GI; DCN

MC CPI: A12-V01; B04-C01C; B04-C01D;
 B04-C01E; B04-C01F; B04-C01G;
 B04-C03C; B04-N02A; B04-N02B; B14-F01; B14-F02B

L74 ANSWER 3 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2003-569409 [53] WPIX

DNC C2003-153717

TI New amphiphilic ion pair complexes of pharmaceutical or cosmetic active agents, with acyl-aminoacids, having good membrane penetration properties and high bioavailability.

DC B05 D21

IN CALVET, N
 PA (PHYS-N) PHYSICA SARL
 CYC 103
 PI WO 2003055528 A2 20030710 (200353)* FR 15 A61K047-48 <--
 RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU
 MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
 RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA
 ZM ZW
 FR 2834215 A1 20030704 (200355) A61K031-195 <--
 AU 2002364684 A1 20030715 (200421) A61K047-48 <--
 EP 1458415 A2 20040922 (200462) FR A61K047-48 <--
 R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC
 MK NL PT RO SE SI SK TR
 ADT WO 2003055528 A2 WO 2002-FR4561 20021224; FR 2834215 A1 FR 2001-16936
 20011227; AU 2002364684 A1 AU 2002-364684 20021224; EP 1458415 A2 EP
 2002-805808 20021224, WO 2002-FR4561 20021224
 FDT AU 2002364684 A1 Based on WO 2003055528; EP 1458415 A2 Based on WO
 2003055528
 PRAI FR 2001-16936 20011227
 IC ICM A61K031-195; A61K047-48
 AB WO2003055528 A UPAB: 20030820
 NOVELTY - A new compound (I) for pharmaceutical or cosmetic use comprises
 an amphiphilic ion pair complex formed from: (A) an acyl-amino acid; and
 (B) a biologically active molecule useful in therapeutic or cosmetic
 treatment.
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
 (1) dispersion system comprising a hydrophilic internal
 dispersed phase containing (I) and a lipophilic continuous
 phase; and
 (2) preparation of (I).
 USE - (I) are amphiphilic derivatives of the parent active agents
 (B), which readily cross biological membranes (thus having increased
 bioavailability) and/or protect (B) against excessively rapid
 bioconversion in the body (thus increasing the half-life in the body). (B)
 are specifically organic molecules, peptides with 2-20 aminoacids,
 nucleotides, genes, polypeptides, proteins, hormones or antigens, e.g.
 amoxicillin, losartan, pravastatin, diclofenac, lidocaine, vancomycin,
 spiramycin, neomycin, colistin, cimetidine, ranitidine, insulin,
 vasopressin, calcitonin, angiotensin, secretin, heparin, growth hormone,
 erythropoietin, parathyroid hormone or filgastrin.
 ADVANTAGE - Use of (A) as the complexing agent provides amphiphilic
 (rather than lipophilic) complexes (I), which are soluble in
 hydrophilic (specifically aqueous) media and can therefore be used
 in aqueous solutions or in the dispersed phase of water-in-oil emulsions.
 Dwg.0/0
 FS CPI
 FA AB; DCN
 MC CPI: B02-A; B02-N; B02-P03; B02-S; B02-V; B02-V01; B04-B03B;
 B04-C01B; B04-C02E; B04-J03A; B04-J04A; B04-N04;
 B04-N06; B07-A01; B07-D09; B07-D13; B10-B02; B10-B02A; B10-B02B;
 B10-B02F; B10-C04A; B10-C04E; B12-M05; B14-R01; D08-B
 L74 ANSWER 4 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
 AN 2003-221302 [21] WPIX
 DNC C2003-056080
 TI Monodispersed mixture of conjugates useful in treatment of disease e.g.
 diabetes comprises drug coupled to oligomer containing polyalkylene glycol
 moiety.
 DC A96 B04 D16
 IN ANSARI, A M; EKWURIBE, N N; ODENBAUGH, A L;
 PRICE, C H
 PA (NOBE-N) NOBEX CORP; (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N;
 (ODEN-I) ODENBAUGH A L; (PRIC-I) PRICE C H
 CYC 101
 PI WO 2002098446 A1 20021212 (200321)* EN 101 A61K038-02 <--
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
 NL OA PT SD SE SL SZ TR TZ UG ZM ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
 RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
 ZW
 BR 2001006401 A 20030211 (200321) A61K047-48 <--

JP 2003104913 A 20030409 (200333) 308 A61K047-48 <--
 US 2003228275 A1 20031211 (200382) A61K038-00 <--
 EP 1404355 A1 20040407 (200425) EN A61K038-02 <--
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR
 AU 2002310289 A1 20021216 (200452) A61K038-02 <--
 ADT WO 2002098446 A1 WO 2002-US17567 20020604; BR 2001006401 A BR 2001-6401
 20011011; JP 2003104913 A JP 2001-317307 20011015; US 2003228275 A1 US
 2001-873797 20010604; EP 1404355 A1 EP 2002-737357 20020604, WO
 2002-US17567 20020604; AU 2002310289 A1 AU 2002-310289 20020604
 FDT EP 1404355 A1 Based on WO 2002098446; AU 2002310289 A1 Based on WO
 2002098446
 PRAI US 2001-873797 20010604
 IC ICM A61K038-00; A61K038-02; A61K047-48
 ICS A61K031-765; A61K038-17; A61K038-18;
 A61K038-19; A61K038-22; A61K038-23;
 A61K038-28; A61K039-02; A61K039-12; A61K039-385; A61K047-34;
 A61P005-00; A61P043-00; C07K001-107; C07K001-113;
 C07K002-00; C07K014-475; C07K014-52;
 C07K014-575; C07K014-585
 AB WO 200298446 A UPAB: 20030328
 NOVELTY - A substantially monodispersed mixture of conjugates comprises a
 drug coupled to an oligomer (a) containing a polyalkylene glycol moiety
 (b).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for
 synthesizing a monodispersed mixture of conjugate, that involves:

(i) reacting a monodispersed mixture containing compounds of formula
 $R1(OC2H4)m-O-X+$ (I) with a substantially monodispersed mixture containing
 compounds of formula $R2(OC2H4)q-OMs$ (II) to form a monodispersed mixture
 comprising polymers of formula $R2(OC2H4)m+q-OR1$ (III);

(ii) activating (III) to form a monodispersed mixture of activated
 polymers capable of reacting with a drug; and

(iii) reacting the monodispersed mixture of activated polymers with a
 monodispersed mixture of drugs to form a monodispersed mixture of
 conjugates comprising drug coupled to an oligomer containing polyethylene
 glycol with m+p subunits.

R1 and R2 = H or lipophilic moiety;

m, q = 1 - 25; and

X+ = positive ion.

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - None given.

USE - In the treatment of disease states e.g. insulin deficiency.

Male CF-1 mice were housed in a room. Mice were acclimated to housing
 conditions for 48 - 72 hours prior to the day of experiment. Prior to
 dosing, mice were fasted overnight and water was provided ad libitum. Mice
 were distributed into groups of five animals per time point and were
 administered a single oral dose of a PEG7-octyl-(sCT), diconjugate (Octyl
 Di) (test) or salmon calcitonin (sCT or Calcitonin) for comparison
 purposes. Oral doses were administered at 10 ml/kg in a phosphate-buffered
 PEG7-octyl-sCT, diconjugate formulation. The buffered formulation was
 prepared by adding phosphate buffer (80 mL) in a beaker. The sodium
 cholate was added to the phosphate buffer with stirring until dissolved.
 The deoxy cholate was then added and stirring was continued until
 dissolved. The PEG7-octyl-sCT, diconjugate, solution was added. The
 remaining phosphate buffer was added to achieve a final weight of 100 g.
 Dose-response curves were constructed. At appropriate time points, mice
 were ether-anesthetized, the vena cavae exteriorized, and blood samples
 were obtained. Blood aliquots were clotted at 22 deg. C for 1 hour, and
 the sera removed and pipetted into a clean receptacle. Total serum calcium
 was determined for each animal. Serum calcium data were plotted and
 pharmacokinetic parameters determined. Means and standard deviations (or
 standard errors) were calculated and plotted to determine effect
 differences among dosing groups. The % baseline calcium drop at 2 micro
 g/kg dose for the test was 21%. The in vitro activity of PEG7-octyl-sCT
 and PEG7-decyl-sCT mono- and diconjugates, the stearate-PEG6-sCT,
 diconjugate, and stearate-PEG8-sCT, diconjugate, appeared to have in vivo
 activity that was comparable with the in vivo activity observed for the
 PEG7-octyl-sCT and PEG7-decyl-sCT, mono- and di-conjugates. The improved
 in vivo activity of the stearate containing conjugates indicated that
 these conjugates were undergoing hydrolysis in vivo to provide an active
 salmon calcitonin or active salmon calcitonin-PEG conjugate.

ADVANTAGE - The mixture exhibits greater in vivo/in vitro activity
 than the in vivo/in vitro activity of the polydispersed mixture of
 drug-oligomer conjugates having same number of average molecular weight as
 the mixture. The mixture has increased resistance to degradation by
 chymotrypsin when compared to the resistance to degradation by

chymotrypsin of a polydispersed mixture of insulin drug-oligomer conjugate mixture having same number average molecular weight as the mixture. The mixture has inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of insulin drug-oligomer conjugates having same number average molecular weight as the mixture.

Dwg. 0/43

FS CPI
FA AB; GI; DCN
MC CPI: A12-V01; B04-C01; B04-C03;
B04-C03C; B04-H01; B04-J01; B04-N01; B04-N02; B04-N03;
B14-S04; D05-H12D

L74 ANSWER 5 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2003-210058 [20] WPIX

DNC C2003-053443

TI Monodispersed mixture of conjugates useful in the treatment of diabetes comprises an insulin drug coupled to an oligomer containing a polyethylene glycol moiety.

DC A25 A96 B04

IN ANSARI, A M; EKWURIBE, N N; ODENBAUGH, A L;

PRICE, C H; RADHAKRISHNAN, B

PA (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (ODEN-I) ODENBAUGH A L;

(PRIC-I) PRICE C H; (RADH-I) RADHAKRISHNAN B; (NOBE-N) NOBEX CORP

CYC 101

PI WO 2002098232 A1 20021212 (200320)* EN 64 A01N061-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
ZW

US 2003027748 A1 20030206 (200320) A61K038-28 <--

BR 2001006851 A 20030408 (200329) A61K038-28 <--

JP 2003113113 A 20030418 (200335) 182 A61K038-28 <--

EP 1404178 A1 20040407 (200425) EN A01N061-00

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR

KR 2004004692 A 20040113 (200434) A61K038-28 <--

AU 2002310291 A1 20021216 (200452) A01N061-00

ADT WO 2002098232 A1 WO 2002-US17574 20020604; US 2003027748 A1 US 2001-873899

20010604; BR 2001006851 A BR 2001-6851 20011011; JP 2003113113 A JP

2001-316998 20011015; EP 1404178 A1 EP 2002-737359 20020604, WO

2002-US17574 20020604; KR 2004004692 A KR 2003-715910 20031204; AU

2002310291 A1 AU 2002-310291 20020604

FDT EP 1404178 A1 Based on WO 2002098232; AU 2002310291 A1 Based on WO

2002098232

PRAI US 2001-873899 20010604

IC ICM A01N061-00; A61K038-28

ICS A01N037-18; A61K031-00; A61K038-00; A61K047-34;

A61K047-48; A61P003-10; A61P005-50; C07K014-62

AB WO 200298232 A UPAB: 20030324

NOVELTY - A substantially monodispersed mixture of conjugates comprising an insulin drug coupled to an oligomer (a) containing a polyethylene glycol moiety (b), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a substantially monodispersed mixture of conjugates (A') comprising human insulin covalently coupled at Lys-B29 of the human insulin to the carboxylic acid moiety of a carboxylic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated polyethylene glycol having at least 7 polyethylene glycol subunits; and

(2) a method of synthesizing a monodispersed mixture of conjugates comprising:

(i) reacting a monodispersed mixture containing compounds of formula R1(OC2H4)m-O-X+ (I) with a substantially monodispersed mixture comprising compound of formula R2(OC2H4)n1-OMs (II) to provide a monodispersed mixture comprising polymers of formula R2(OC2H4)m+n1-OR1 (III);

(ii) activating (III) to provide a monodispersed mixture of activated polymers capable of reacting with insulin drug; and

(iii) reacting the monodispersed mixture of activated polymers with a monodispersed mixture of drugs to provide a monodispersed mixture of conjugates comprising insulin drug coupled to an oligomer containing polyethylene glycol with m+n1 subunits.

R, R2 = H or lipophilic moiety;

m, n1 = 1-25;

X+ = positive ion.

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - None given.

USE - The mixture is used in the treatment of insulin deficiency in a subject (claimed).

ADVANTAGE - The mixture exhibits greater in vivo/vitro activity than the in vivo/vitro activity of the polydispersed mixture of insulin drug-oligomer conjugates having same number of average molecular weight as the mixture respectively. The mixture has increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of insulin drug-oligomer conjugate mixture having same number average molecular weight as the mixture. The mixture has inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of insulin drug-oligomer conjugates having same number average molecular weight as the mixture.

Dwg. 0/21

FS CPI

FA AB; GI; DCN

MC CPI: A12-V01; B04-C03C; B04-J03A; B14-S04

L74 ANSWER 6 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2003-183863 [18] WPIX

DNC C2003-048349

TI Insulin composition for pulmonary administration in the treatment of diabetes comprises a conjugate of insulin covalently coupled to a non-naturally occurring hydrophilic polymer.

DC A96 B04

IN BUECHE, B; HARRIS, J M; KUO, M; LEACH, C; PATTON, J S; PERKINS, K; KUO, M K

PA (NEKT-N) NEKTAR THERAPEUTICS; (NEKT-N) NEKTAR THERAPEUTICS AL CORP; (BUEC-I) BUECHE B; (HARR-I) HARRIS J M; (KUOM-I) KUO M; (LEAC-I) LEACH C; (PAT-I) PATTON J S; (PERK-I) PERKINS K; (INHA-N) INHALE THERAPEUTIC SYSTEMS INC; (SHEA-N) SHEARWATER CORP

CYC 101

PI WO 2002094200 A2 20021128 (200318)* EN 43 A61K000-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
ZW

US 2003118510 A1 20030626 (200343) A61L009-04

US 2003216542 A1 20031120 (200377) C07K005-00 <--

NO 2003005157 A 20040112 (200412) A61L000-00

EP 1395294 A2 20040310 (200418) EN A61L009-04

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR

KR 2003097876 A 20031231 (200427) A61K047-48 <--

SK 2003001553 A3 20040608 (200441) A61K009-24

AU 2002303869 A1 20021203 (200452) A61K000-00

BR 2002009896 A 20040817 (200457) A61L009-04

CZ 2003003182 A3 20040915 (200462) A61L009-04

ADT WO 2002094200 A2 WO 2002-US16464 20020521; US 2003118510 A1 Provisional US 2001-292423P 20010521, US 2002-154057 20020521; US 2003216542 A1 Provisional US 2001-292423P 20010521, Cont of US 2002-154057 20020521, US 2003-405190 20030401; NO 2003005157 A WO 2002-US16464 20020521, NO 2003-5157 20031120; EP 1395294 A2 EP 2002-731931 20020521, WO 2002-US16464 20020521; KR 2003097876 A KR 2003-714954 20031117; SK 2003001553 A3 WO 2002-US16464 20020521, SK 2003-1553 20020521; AU 2002303869 A1 AU 2002-303869 20020521; BR 2002009896 A BR 2002-9896 20020521, WO 2002-US16464 20020521; CZ 2003003182 A3 WO 2002-US16464 20020521, CZ 2003-3182 20020521

FDT EP 1395294 A2 Based on WO 2002094200; SK 2003001553 A3 Based on WO 2002094200; AU 2002303869 A1 Based on WO 2002094200; BR 2002009896 A Based on WO 2002094200; CZ 2003003182 A3 Based on WO 2002094200

PRAI US 2001-292423P 20010521; US 2002-154057 20020521;
US 2003-405190 20030401

IC ICM A61K000-00; A61K009-24; A61K047-48; A61L000-00; A61L009-04;
C07K005-00

ICS A61K038-00; A61K038-16; A61K038-28

AB WO 200294200 A UPAB: 20030317

NOVELTY - An insulin composition for pulmonary administration comprises a conjugate of insulin (A) covalently coupled to at least one molecule of a non-naturally occurring hydrophilic polymer (B) and an

excipient.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

- (1) Method (M1) for delivering (A) involving administering aerosolized insulin composition by inhalation for deposition in and absorption from the lungs of the subject; and
- (2) Method (M2) for providing non-immunogenic insulin composition to the lungs involving covalently coupling (A) to at least one (B), and administering the composition to the lungs by inhalation. The insulin passes through the lung and enters into the blood circulation.

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - None given.

USE - For pulmonary delivery of insulin to the lungs of mammalian subject (claimed) in the treatment of diabetes mellitus, type I and type II diabetes.

ADVANTAGE - The composition has an absolute pulmonary bioavailability greater than (preferably greater than 15%, especially greater than 30%, particularly at least twice) that of native insulin. The composition has Tmax of at least three times (preferably at least five times) that of native insulin. The composition elevates the blood level of insulin for at least 8 (preferably at least 10, especially at least 12) hours post administration. The composition increases the serum level of insulin at least 2 times greater than the basal level within 1 hour post administration.

Dwg. 0/14

FS CPI
FA AB; DCN
MC CPI: A05-H01B; A10-E01; A12-V01; B04-C03C; B04-J03A;
B12-M01A; B12-M01B; B14-S04

L74 ANSWER 7 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2003-046722 [04] WPIX

DNC C2003-011825

TI Treatment of diabetes mellitus using an insulin-polypeptide derivative.

DC A96 B04

IN EKWURIBE, N N; FILBEY, J A; PRICE, C H; STILL, J G;

ANSARI, A M; ODENBAUGH, A L; RADHAKRISHNAN, B

PA (EKWU-I) EKWURIBE N N; (FILB-I) FILBEY J A; (PRIC-I) PRICE C H; (STIL-I) STILL J G; (NOBE-N) NOBEX CORP

CYC 101

PI WO 2002065985 A2 20020829 (200304)* EN 114 A61K000-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
ZW

US 2003050228 A1 20030313 (200321) A61K038-28 <--

AU 2002244020 A1 20020904 (200427) A61K000-00

EP 1409006 A2 20040421 (200427) EN A61K038-28 <--

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR

JP 2004527487 W 20040909 (200459) 187 A61K038-28 <--

KR 2004043113 A 20040522 (200460) A61K038-28 <--

ADT WO 2002065985 A2 WO 2002-US4440 20020214; US 2003050228 A1 Provisional US

2001-269198P 20010215; US 2002-75097 20020213; AU 2002244020 A1 AU

2002-244020 20020214; EP 1409006 A2 EP 2002-709541 20020214, WO

2002-US4440 20020214; JP 2004527487 W JP 2002-565546 20020214, WO

2002-US4440 20020214; KR 2004043113 A KR 2003-710645 20030813

FDT AU 2002244020 A1 Based on WO 2002065985; EP 1409006 A2 Based on WO

2002065985; JP 2004527487 W Based on WO 2002065985

PRAI US 2002-347713P 20020111; US 2001-269198P 20010215;

US 2002-75097 20020213

IC ICM A61K000-00; A61K038-28

ICS A61K047-48; A61P003-10; C07K014-62

AB WO 2002065985 A UPAB: 20030117

NOVELTY - Treatment of diabetes mellitus comprises orally administering an insulin-polypeptide derivative (I) to a patient within one hour of ingestion of a meal so that it provides an insulin drug concentration in portal vein blood between 10 and 1,000 U/ml within about 60 minutes of administration.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the use of (I) in the manufacture of an oral medicament for the treatment of diabetes mellitus.

ACTIVITY - Antidiabetic.

Pancreactomized and normal, fasted dogs were orally administered with

a polydispersed mixture of insulin polypeptide -NH-C(O)-(CH₂)₅(OC₂H₄)₇OC₃H₇ (1 mg/kg). At the given dosage of the insulin, all the dogs required glucose rescue, due to marked symptomatic hypoglycemia.

MECHANISM OF ACTION - None given.

USE - In the treatment of diabetes mellitus (claimed).

ADVANTAGE - (I) provides an insulin drug concentration in portal vein blood from about 10 - 1000 U/ml in about 60 (preferably 30) minutes of administration; provides maximum insulin drug concentration in peripheral blood in about 60 minutes; stabilizes peripheral glucose concentration to plus or minus 50% of average peripheral glucose concentration in 30 - 60 minutes; clears the bloodstream of a patient in about 4 hours; and reduces hepatic glucose production in a patient by at least 25% in about 90 minutes. At least 25% of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed in about 120 minutes after injection of the meal (all claimed).

Dwg.1a/20

FS CPI

FA AB; GI; DCN

MC CPI: A12-V01; B04-C03C; B04-J03A; B14-S04

L74 ANSWER 8 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2002-657431 [70] WPIX

DNC C2002-184421

TI New amide-linked mono, di and tri-saccharide-lipoamino acid complex useful in drug delivery.

DC B07 C07

IN FALCONER, R; TOTH, I; DE CRUZ, S E; MCGEARY, R P; ROSS, B P

PA (ALCH-N) ALCHEMIA PTY LTD; (DCRU-I) DE CRUZ S E; (FALC-I) FALCONER R;

(MCGE-I) MCGEARY R P; (ROSS-I) ROSS B P; (TOTH-I) TOTH I

CYC 100

PI WO 2002053572 A1 20020711 (200270)* EN 66 C07H015-04

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
ZW

AU 2002216843 A1 20020716 (200427) C07H015-04

US 2004176281 A1 20040909 (200459) A61K038-16 <--

ADT WO 2002053572 A1 WO 2002-AU5 20020103; AU 2002216843 A1 AU 2002-216843
20020103; US 2004176281 A1 CIP of WO 2002-AU5 20020103, US 2003-676436
20030630

FDT AU 2002216843 A1 Based on WO 2002053572

PRAI GB 2001-115 20010104

IC ICM A61K038-16; C07H015-04

ICS A61K031-715; A61K038-14; A61K047-26; A61K047-36;

A61K047-48; C07H015-12; C07K009-00

AB WO 200253572 A UPAB: 20021031

NOVELTY - Amide-linked mono, di and tri-saccharide-lipoamino acid complex (I) is new.

DETAILED DESCRIPTION - Amide-linked mono, di and tri-saccharide-lipoamino acid complex of formula r(D(nz))pQ (I) is new.

Q = carrier compound of formula ((Wq-S-X-L)(my));

D = therapeutically useful molecule;

r = 0 or not more than 0;

p = not more than 1;

n, m = not more than 1 and represent overall magnitude of the charge on the molecule;

z, y = positive or negative charges;

X = covalent bond or is a linker group selected from 2-14 atom spacers;

S = mono- or oligosaccharide;

L = lipidic moiety

W = 3-10C (hetero)alkyl (optionally branched) and is substituted with at least one functional group which is charged or carries a charge under physiological conditions; and

q = 0 when W is absent or ranges from 3 to the number of hydroxyls available for substitution on the mono- or oligosaccharide.

INDEPENDENT CLAIMS are also included for the following:

(1) preparation of (I);

(2) delivering a therapeutically useful molecule comprising administering (I).

ACTIVITY - Cytostatic; Nootropic; Neuroprotective; Cardiant; Hypotensive; Antiarteriosclerotic.

MECHANISM OF ACTION - None given in the source material.

USE - For treating or preventing a pathological condition and in the delivery of a therapeutically useful molecule (claimed), for treating neoplasm, cancers (e.g. cancers of breast, lung etc), fibrotic disorder, disorder of the central nervous system (e.g. Alzheimer's disease), dementia, memory loss, motor neuron disease, disorder of cardiovascular system (e.g. cardiac hypertrophy, congestive heart failure, hypertension, hormonal imbalance, atherosclerosis), and disorders of development and growth (including disorders of glucose and fat metabolism).

ADVANTAGE - The complex is as an ionic delivery system, in which the drug molecule and the delivery system form an ionic complex. The complex does not require the chemical conjugation of the drug molecule and therefore does not alter the pharmaceutical properties of the drug molecule. The complex can also be used to target either passive or active transport mechanisms and is readily optimized for hydrophilic drug molecules, peptides and proteins and offers significant benefits in terms of regulatory approval.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B04-C02V; B14-F01; B14-F02; B14-H01B; B14-J01; B14-K01;
B14-S04; C04-C02V; C14-F01; C14-F02; C14-H01B; C14-J01;
C14-K01; C14-S04

L74 ANSWER 9 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2002-519168 [55] WPIX

DNC C2002-146835

TI New synthetic regulatory compound useful for combating infections by pathogens comprises non-natural nucleic binder, a regulatory moiety and a linker.

DC B03 C02 D16

IN ANSARI, A; DERVAN, P; MAPP, A; PTASHNE, M

PA (CALY) CALIFORNIA INST OF TECHNOLOGY; (SLOK) SLOAN KETTERING INST CANCER

RES

CYC 88

PI WO 2002034295 A1 20020502 (200255)* EN 103 A61K047-48 <--

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ

NL OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB

GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU

LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR

TT UA UG US UZ VN YU ZA ZW

AU 2001013481 A 20020506 (200257)

A61K047-48 <--

ADT WO 2002034295 A1 WO 2000-US29617 20001027; AU 2001013481 A WO 2000-US29617 20001027, AU 2001-13481 20001027

FDT AU 2001013481 A Based on WO 2002034295

PRAI WO 2000-US29617 20001027

IC ICM A61K047-48

ICS A61K049-00

AB WO 200234295 A UPAB: 20020829

NOVELTY - A synthetic regulatory compound (I) or its salt comprises a non-natural nucleic acid binding moiety (a), a regulatory moiety (b) and a linker (c) connecting (b) to (c).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a cell in vitro or in vivo comprising (I);

(2) a complex comprising (I) complexed with a double-stranded DNA;

(3) forming the complex involving exposing a composition (preferably a cell) containing a double-stranded DNA containing target sequence to (I);

(4) regulating transcription of a regulatable gene in vitro or in vivo involving exposing a double-stranded DNA encoding the regulatable gene to (I) capable of regulating its transcription under transcription condition; and

(5) screening (I) in vitro or in vivo involving exposing the double-stranded DNA encoding the regulatable gene (preferably marker gene) to several test compounds and determining whether

the test compound regulates expression of the regulatable gene.

ACTIVITY - Fungicide; Anti-bacterial; Virucide; Cytostatic; Vasotropic; Antipsoriatic; Antiarteriosclerotic; Hypotensive; Dermatological; Antidepressant; Antiinflammatory; Antirheumatic; Antiarthritic; Hepatotropic; Anti allergic; Antiulcer; Cardiovascular-General; Immunosuppressive; Neuroprotective; Antidiabetic; Thyromimetic.

No supporting data provided.

MECHANISM OF ACTION - Gene expression inhibitor; Gene activator; Modulator; Expression of specific gene regulator.

The synthetic regulatory compounds used employed polyamide molecules

as non-natural nucleic acid binding moieties. The compounds were tested a cell line of SKOV (a cisplatin resistant human ovarian cancer cell line). The compounds were also tested for their ability to activate a transiently transfected reporter gene the expression of which could be up-regulated by activation of a promoter functionally associated with one DR5 target site. The reporter gene carried by the cells comprised a minimal HSV TK promoter driving the expression of a luciferase gene. Promoter activity was regulated by a consensus DR5 site approximately 50 bp upstream of the TK promoter. The DR5 site comprised a direct repeat of two consensus hexameric sequences separated by five nucleotides, the identity of which was irrelevant. One of the consensus hexameric nucleotide sequences in the DR5 site was 5'-AGGTCA-3', which also corresponded to an estrogen receptor half site. The polyamide moieties of the synthetic regulatory compounds used in this experiment targeted the nucleotide sequence 5'-WGGWCA-3', and were fused via a PEG linker at the C-terminal tail to either the L- or the D- form of a VP2 activating region (Amv154 and Amv155 respectively). Prior to testing these two conjugates on reporter cells, these compounds were tested for their ability to activate transcription in standard cell-free yeast system that comprised a reporter construct having three tandem 5'-AGGTCA-3' sites located 40 bp upstream of the AdML TATA:G-less cassette. The in vitro transcription experiments were performed. The Amv151 polyamide alone did not stimulate transcription over basal conditions. The synthetic regulatory compound Amv154 (PA-1L-VP2) activated transcription about 12 fold, and Amv155 (PA-1L-D-VP2) activated transcription about ten-fold in the in vitro assays. The observed levels of activation were consistent with the fact that only three half sites, rather than three complete palindromes, were used in the reporter construct employed in the in vitro transcription assays. The cells used for the cell permeability and cell-based reporter assays were passaged twice and then grown overnight in 6-well plates to sub-confluency in CO2 incubators. Two micrograms of DR5-Luc DNA and 0.5 micrograms of CMV- beta gal were transfected in each of the wells. One well on each plate contained no reporter construct, and one contained a strong CMV promoter driving the Luc reporter gene to check for transfection efficiency. SKOV cells were transfected using DOTAP (a cationic lipid transfection system). After DNA addition, the cells were incubated for 12 hours and then washed with fresh DMEM media containing 10% charcoal-stripped Fetal Bovine Serum. Cells were then allowed to recover for 12 hours in 2 ml of DMEM+15% FBS (stripped). After washing out this media, cells were supplied with 1 ml of DMEM+10% FBS (stripped) containing Amv151, Amv154, or Amv155 at 1 mu M concentrations. Luciferase activity was measured using standard luminomitor techniques. For reporter of cells alone, conjugate (none given), the luciferase activity was 464. For reporter of CMV-Luc and conjugate (none given), the luciferase activity was 859304. For reporter of DR5-Luc without any conjugate, the luciferase activity was 828117. For reporter of DR5-Luc with conjugate of Amv151/Amv154/Amv155, the luciferase activity was 400439/570395/703533 and the normalized activation was 1/1.425/1.75 respectively.

USE - In composition such as liquid composition or dry composition; and in a cell (e.g. animal cell, plant cell, bovine, canine, equine, feline, murine, ovine, porcine, primate cell or human cell) also in regulating transcription of a regulatable gene (claimed). For combating infections by pathogens including protozoa, virus; for treating eukaryotic organisms such as plants such as agricultural crop and animals such as bovines, canine, equine, feline, ovine etc; to modulate physiological processes in vivo. In the treatment of cancer, restenosis, psoriasis, lymphopoiesis, atherosclerosis, pulmonary fibrosis, primary pulmonary hypertension, neurofibromatosis, acoustic neuroma, tuberous sclerosis, keloid, fibrocystic breast, polycystic ovary and kidney, scleroderma, inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, myelodysplasia, cirrhosis, esophageal stricture, sclerosing cholangitis, retroperitoneal fibrosis, skin graft rejection, allergic response, psychosis, sleep regulation, immune response, mucosal ulceration, withdrawal symptoms associated with termination of substance use, pathogenesis of liver injury, cardiovascular processes, neuronal processes, autoimmune diseases; for down-regulating the gene coding for the RNA and protein components of telomerase; and in agricultural and medicinal applications.

ADVANTAGE - (I) is cell permeable. (I) exhibits good anti-fungal and anti-bacterial (Gram-positive, Gram-negative, aerobic and anaerobic) properties.

Dwg. 0/17

FS CPI

FA AB; DCN

MC CPI: B04-E01; B04-F01; B11-C08; B12-K04; B14-A02; B14-C09B; B14-F01; B14-F02; B14-F02B; B14-F07; B14-G02C; B14-H01; B14-J01; B14-K01;

B14-N10; B14-N12; B14-N17C; B14-S04; B14-S06; C04-E01;
 C04-F01; C11-C08; C12-K04; C14-A02; C14-C09B; C14-F01;
 C14-F02; C14-F02B; C14-F07; C14-G02C; C14-H01; C14-J01; C14-K01;
 C14-N10; C14-N12; C14-N17C; C14-S04; C14-S06; D05-H09

L74 ANSWER 10 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
 AN 2002-268849 [31] WPIX
 CR 1999-105499 [09]; 2002-280618 [32]; 2003-669500 [63]
 DNN N2002-209278 DNC C2002-079681
 TI Method for treating vaginal or uterine fungal, bacterial, viral and
 parasitic infections comprises intravaginal or transvaginal administration
 of an antifungal, parasiticidal, antibacterial or antiviral agent.
 DC A96 B05 C03 D22 F07 P32 P34
 IN DAUGUSTINE, M A; HARRISON, D C; LIU, J H; D'AUGUSTINE, M A
 PA (UMDU-N) UMD INC
 CYC 95
 PI WO 2002003896 A1 20020117 (200231)* EN 49 A61F006-06
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
 NL OA PT SD SE SL SZ TR TZ UG ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
 DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ
 LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD
 SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
 AU 2001081287 A 20020121 (200234) A61F006-06
 EP 1301150 A1 20030416 (200328) EN A61F006-06
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR
 BR 2001012571 A 20030527 (200344) A61F006-06
 JP 2004508296 W 20040318 (200420) 73 A61K047-48 <--
 MX 2002012819 A1 20030901 (200465) A61F013-00
 ADT WO 2002003896 A1 WO 2001-US41128 20010625; AU 2001081287 A AU 2001-81287
 20010625; EP 1301150 A1 EP 2001-959766 20010625, WO 2001-US41128 20010625;
 BR 2001012571 A BR 2001-12571 20010625, WO 2001-US41128 20010625; JP
 2004508296 W WO 2001-US41128 20010625, JP 2002-508356 20010625; MX
 2002012819 A1 WO 2001-US41128 20010625, MX 2002-12819 20021219
 FDT AU 2001081287 A Based on WO 2002003896; EP 1301150 A1 Based on WO
 2002003896; BR 2001012571 A Based on WO 2002003896; JP 2004508296 W Based
 on WO 2002003896; MX 2002012819 A1 Based on WO 2002003896
 PRAI US 2000-613441 20000711
 IC ICM A61F006-06; A61F013-00; A61K047-48
 ICS A61F013-02; A61F013-20; A61K009-02; A61K009-06; A61K009-08;
 A61K009-10; A61K009-12; A61K009-14; A61K009-20; A61K031-4164
 ; A61K031-4174; A61K031-4178;
 A61K031-4196; A61K031-43; A61K031-496;
 A61K031-513; A61K031-52; A61K031-522;
 A61K031-7048; A61K031-7056; A61K031-7072;
 A61K047-10; A61K047-14; A61K047-28; A61K047-34; A61K047-36;
 A61K047-38; A61L015-16; A61M031-00; A61P015-00; A61P031-04;
 A61P031-10; A61P031-12; A61P033-02
 AB WO 200203896 A UPAB: 20041011
 NOVELTY - A method for treating vaginal or uterine fungal, bacterial,
 viral and parasitic infections is new.
 DETAILED DESCRIPTION - A method for treating vaginal or uterine
 fungal, bacterial, viral and parasitic infections comprises contacting the
 vaginal epithelium with an intravaginal device medicated with an
 intravaginal or transvaginal composition comprising an active agent and an
 excipient. The active agent is an antifungal, parasiticidal, antibacterial
 or antiviral agent or trichomonicide and the excipient comprises a
 lipophilic or hydrophilic carrier, a mucoadhesive and a
 penetration enhancer or sorption promoter.
 INDEPENDENT CLAIMS are also included for the following:
 (1) a composition for intravaginal or transvaginal delivery for the
 treatment of fungal, viral, bacterial or parasitic infections comprising
 miconazole, terconazole, isoconazole, fenticonazole, fluconazole,
 nystatin, ketoconazole, clotrimazole, butoconazole, econazole,
 metronidazole, clindamycin, 5-fluoracil, aciclovir, AZT, famovir,
 penicillin, tetracycline or erythromycin in a vaginal suppository,
 bioadhesive tablet, bioadhesive microparticle, cream, lotion, foam,
 ointment, paste, solution or gel; and
 (2) a device for intravaginal or transvaginal delivery of antifungal,
 antiviral, antibacterial or parasiticidal agents comprising a tampon,
 tampon-like device, vaginal ring, vaginal pessary, vaginal cup, vaginal
 tablet, vaginal suppository, vaginal sponge, vaginal bioadhesive tablet or
 vaginal bioadhesive microparticle comprising the agent as a cream, lotion,
 foam, ointment, solution or gel.
 ACTIVITY - Fungicide; Antibacterial; Virucide; Antiparasitic;

Uropathic; Gynecological.

MECHANISM OF ACTION - None given in the source material.

USE - The method is useful for treating vaginal or uterine fungal, bacterial, viral and parasitic infections.

Dwg.0/19

FS CPI GMPI

FA AB; DCN

MC CPI: A12-V01; A12-V03A; B02-E; B02-T; B04-C03C;

B06-D02; B06-D09; B07-H; B10-C04E; B10-E04C; B12-M02; B12-M03;
B12-M07; B12-M08; B12-M09; B12-M11; B14-A01; B14-A02; B14-A03;
B14-A03D; B14-A04; C02-E; C02-T; C04-C03C; C06-D02;
C06-D09; C07-H; C10-C04E; C10-E04C; C12-M02; C12-M03; C12-M07;
C12-M09; C12-M11; C14-A01; C14-A02; C14-A03; C14-A03D; C14-A04;
D09-A01; F04-C01; F04-E04

L74 ANSWER 11 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2001-496568 [54] WPIX

DNC C2001-149074

TI Compositions useful in treatment of obesity include luminal
cholecystokinin releasing factor coupled to an amphiphilic polymer, which
exhibits improved pharmacokinetic properties.

DC A25 A96 B04 D16

IN EKWURIBE, N N; EKWURIBE, N

PA (NOBE-N) NOBEX CORP; (EKWU-I) EKWURIBE N

CYC 95

PI WO 2001041812 A2 20010614 (200154)* EN 49 A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001020875 A 20010618 (200161) A61K047-48 <--
BR 2000016339 A 20020827 (200265) A61K047-48 <--
NO 2002002793 A 20020813 (200266) A61K000-00
EP 1237580 A2 20020911 (200267) EN A61K047-48 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR
CZ 2002001990 A3 20021113 (200282) A61K047-48 <--
KR 2002068053 A 20020824 (200309) A61K047-48 <--
JP 2003516366 W 20030513 (200334) 59 A61K047-48 <--
HU 2003000133 A2 20030528 (200341) A61K047-48 <--
CN 1434725 A 20030806 (200366) A61K047-48 <--
US 6638906 B1 20031028 (200372) A01N037-18
MX 2002005885 A1 20021101 (200376) A61K047-48 <--
ZA 2002004603 A 20031126 (200402) 71 A61K000-00
NZ 519489 A 20040130 (200414) A61K047-48 <--
US 2004092449 A1 20040513 (200432) A61K038-17 <--

ADT WO 2001041812 A2 WO 2000-US33592 20001211; AU 2001020875 A AU 2001-20875
20001211; BR 2000016339 A BR 2000-16339 20001211, WO 2000-US33592
20001211; NO 2002002793 A WO 2000-US33592 20001211, NO 2002-2793 20020612;
EP 1237580 A2 EP 2000-984215 20001211, WO 2000-US33592 20001211; CZ
2002001990 A3 WO 2000-US33592 20001211, CZ 2002-1990 20001211; KR
2002068053 A KR 2002-707500 20020612; JP 2003516366 W WO 2000-US33592
20001211, JP 2001-543156 20001211; HU 2003000133 A2 WO 2000-US33592
20001211, HU 2003-133 20001211; CN 1434725 A CN 2000-818964 20001211; US
6638906 B1 US 1999-459443 19991213; MX 2002005885 A1 WO 2000-US33592
20001211, MX 2002-5885 20020612; ZA 2002004603 A ZA 2002-4603 20020607; NZ
519489 A NZ 2000-519489 20001211, WO 2000-US33592 20001211; US 2004092449
A1 Div ex US 1999-459443 19991213, US 2003-633966 20030804

FDT AU 2001020875 A Based on WO 2001041812; BR 2000016339 A Based on WO
2001041812; EP 1237580 A2 Based on WO 2001041812; CZ 2002001990 A3 Based
on WO 2001041812; JP 2003516366 W Based on WO 2001041812; HU 2003000133 A2
Based on WO 2001041812; MX 2002005885 A1 Based on WO 2001041812; NZ 519489
A Based on WO 2001041812; US 2004092449 A1 Div ex US 6638906

PRAI US 1999-459443 19991213; US 2003-633966 20030804

IC ICM A01N037-18; A61K000-00; A61K038-17; A61K047-48

ICS A61P003-04; C07K014-595; C08G063-48; C08G063-91

AB WO 200141812 A UPAB: 20040210

NOVELTY - Compositions which include luminal cholecystokinin releasing
factor (LCRF) coupled to amphiphilic polymers are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the
following:

(1) LCRF composition comprising LCRF coupled with one or more
molecules of a non-naturally occurring polymer. The polymer comprises a
lipophilic group and a hydrophilic polymer group,

therefore imparting both lipophilic and hydrophilic characteristics to the composition so that the composition is soluble in pharmaceutical solvents and is able to interact with biological membranes;

(2) peptide composition comprising LCRF coupled with one or more molecules of a non-naturally occurring polymer which comprises a LM and a hydrophilic moiety. The composition is soluble in aqueous solvents, and the LCRF is active in treatment or prevention of obesity;

(3) LCRF composition comprising LCRF covalently coupled with one or more molecules of a polymer which comprises a linear polyalkylene glycol group and a lipophilic group. The peptide and components are conformationally arranged such that the LCRF has an enhanced in vivo resistance to enzymatic degradation, relative to LCRF alone;

(4) multiligand conjugated LCRF complex comprising a triglyceride backbone group. The LCRF is covalently coupled with the triglyceride backbone group through a polyalkylene glycol spacer group which is bonded at a carbon atom of the triglyceride backbone. At least one fatty acid is covalently attached to a carbon atom of the triglyceride backbone group or is covalently joined through a polyalkylene glycol spacer group;

(5) stable, aqueous-soluble, conjugated LCRF complex which comprises a LCRF conjugatively coupled to a glycolipid group modified with polyethylene glycol;

(6) polysorbate complex comprising a polysorbate group which includes a triglyceride backbone which has a fatty acid group covalently coupled to one of the alpha, alpha' or beta carbon atoms and a polyethylene glycol group covalently coupled to one of the alpha, alpha' or beta carbon atoms. A physiologically active moiety can be covalently bonded to the polyethylene glycol group;

(7) compounds of formula (I):

X = N, O or S;

Y = LCRF or a protein;

n = 3 - 230; and

m = 0 - 20.

ACTIVITY - Anorectic. No biodata is provided.

MECHANISM OF ACTION - Luminal cholecystokinin releasing factor receptor agonist.

USE - The materials are useful for delivery of LCRF to receptors in the gut. LCRF is capable of stimulating release of cholecystokinin, a polypeptide hormone that induces satiety and reduces food intake. The materials may thus be used in treatment or prevention of obesity. Other peptides may be used in place of LCRF in the materials, so that they could be used for delivery of peptides useful in treatment of other disorders.

ADVANTAGE - The materials are stable and soluble in aqueous solutions. They may exhibit prolonged blood circulation and can be conformationally arranged so that the LCRF has enhanced in vivo resistance to enzymatic degradation. The conjugates can also deliver LCRF to receptors in the gut without absorption into the bloodstream.

Dwg.0/3

FS CPI

FA AB; DCN

MC CPI: A10-E08; A12-V01; B04-C03D; B04-H01; B04-J13;
B04-K01; B12-M05; B14-E12; B14-L01; D05-H10

L74 ANSWER 12 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2001-335428 [35] WPIX

CR 2003-040529 [03]

DNC C2001-103553

TI New taxane prodrugs comprising polyethylene glycol units attached to a taxane by a hydrolyzable bond, useful for treating cancers.

DC A25 A96 B02 B07

IN BARTLEY, G S; EKWURIBE, N N; PRICE, C H; PRICE, C; EKWURIBE, N

PA (NOBE-N) NOBEX CORP; (BART-I) BARTLEY G S; (EKWU-I) EKWURIBE N N; (PRIC-I) PRICE C H

CYC 95

PI WO 2001019407 A2 20010322 (200135)* EN 57 A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000069512 A 20010417 (200140) A61K047-48 <--
US 2002013484 A1 20020131 (200210) C07D305-14
US 6380405 B1 20020430 (200235) C07D305-14
NO 2002001212 A 20020513 (200239) A61K000-00
BR 2000013949 A 20020514 (200240) A61K047-48 <--

EP 1214096 A2 20020619 (200240) EN A61K047-48 <--
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI

CZ 2002000929 A3 20020814 (200263) A61K047-48 <--
 JP 2003509386 W 20030311 (200319) 74 A61K031-337 <--
 KR 2002082458 A 20021031 (200319) A61K047-48 <--
 CN 1390142 A 20030108 (200334) A61K047-48 <--
 HU 2003000093 A2 20030528 (200341) A61K047-48 <--
 ZA 2002002040 A 20030827 (200362) 92 A61K000-00 <--
 MX 2002002711 A1 20020801 (200367) A61K047-48 <--
 US 2003203961 A1 20031030 (200372) A61K031-337 <--
 NZ 517680 A 20031219 (200404) A61K047-48 <--

ADT WO 2001019407 A2 WO 2000-US24523 20000907; AU 2000069512 A AU 2000-69512
 20000907; US 2002013484 A1 Provisional US 1999-153579P 19990913, CIP of US
 1999-476974 19991231, US 2001-802739 20010309; US 6380405 B1 Provisional
 US 1999-153579P 19990913, US 1999-476974 19991231; NO 2002001212 A WO
 2000-US24523 20000907, NO 2002-1212 20020312; BR 2000013949 A BR
 2000-13949 20000907, WO 2000-US24523 20000907; EP 1214096 A2 EP
 2000-957966 20000907, WO 2000-US24523 20000907; CZ 2002000929 A3 WO
 2000-US24523 20000907, CZ 2002-929 20000907; JP 2003509386 W WO
 2000-US24523 20000907, JP 2001-523038 20000907; KR 2002082458 A KR
 2002-703277 20020312; CN 1390142 A CN 2000-815507 20000907; HU 2003000093
 A2 WO 2000-US24523 20000907, HU 2003-93 20000907; ZA 2002002040 A ZA
 2002-2040 20020312; MX 2002002711 A1 WO 2000-US24523 20000907, MX
 2002-2711 20020312; US 2003203961 A1 Provisional US 1999-153579P 19990913,
 CIP of US 1999-476974 19991231, Cont of US 2001-802739 20010309, US
 2003-395548 20030324; NZ 517680 A NZ 2000-517680 20000907, WO 2000-US24523
 20000907

FDT AU 2000069512 A Based on WO 2001019407; BR 2000013949 A Based on WO
 2001019407; EP 1214096 A2 Based on WO 2001019407; CZ 2002000929 A3 Based
 on WO 2001019407; JP 2003509386 W Based on WO 2001019407; HU 2003000093 A2
 Based on WO 2001019407; MX 2002002711 A1 Based on WO 2001019407; US
 2003203961 A1 CIP of US 6380405, Cont of US 6541508; NZ 517680 A Based on
 WO 2001019407

PRAI US 1999-476974 19991231; US 1999-153579P 19990913;
 US 2001-802739 20010309; US 2003-395548 20030324

IC ICM A61K000-00; A61K031-337; A61K047-48; C07D305-14
 ICS A61K009-08; A61K009-10; A61K009-14; A61K009-20; A61K009-48;
 A61P013-12; A61P033-06; A61P035-00; A61P035-02; A61P043-00

AB WO 200119407 A UPAB: 20040115
 NOVELTY - New taxane prodrugs comprising polyethylene glycol units
 attached to a taxane by a hydrolyzable bond, useful for treating cancers
 are disclosed.

DETAILED DESCRIPTION - A novel taxane prodrug comprises: (a) at least
 one taxane; and (b) one or more polyethylene (PEG) polymers and/or
 oligomers, each joined to a bonding site on the therapeutic compound by a
 hydrolyzable bond, the PEG polymers and/or oligomers each: (i) comprising
 a straight or branched PEG segment consisting of 2 to 25 PEG units; and
 (ii) optionally comprising a salt-forming moiety.

An INDEPENDENT CLAIM is also included for a taxane prodrug comprising
 a taxane joined by hydrolyzable bond(s) to one or more PEG oligomer(s)
 selected from: formula (II)-(XI): -CO-(CH₂)_n-NR-CH₂CH₂(OC₂H₄)_mOCH₃ (II);
 -CO-(CH₂)_{n1}-CO-NH-(CH₂)_p-NR-CH₂CH₂(OC₂H₄)_mOCH₃ (III);
 -CO-(CH₂)_{n1}-CO-NH-(CH₂)_p-NR-CH₂CH₂(OC₂H₄)_mOCH₃ (IV);
 -CO-(CH₂)_{n1}-CO-NH-(CH₂)_p-NR-CH₂CH₂(OC₂H₄)_mNH₂ (V);
 -CO-(CH₂)_{n1}-CO-NH-(CH₂)_p-NR-CH₂CH₂(OC₂H₄)_mNH₃+X- (VI);
 -CO-(CH₂)_{n1}-CO-NH-(CH₂)_p-NR₁-CH₂CH₂(OC₂H₄)_mNHR₂ (VII);
 -CO-(CH₂)_{n1}-CO-NH-CH₂CH₂(OC₂H₄)_mOCH₂-C(=O)-NH(CH₂)_pN(CH₃)₂ (VIII);
 -CO-(CH₂)_{n1}(OC₂H₄)_mO(CH₂)_{p1}-C(=O)-O-Y+ (IX);
 -CO-(CH₂)_{n2}-NR₁R₂-CH₂CH₂(OC₂H₄)_mOCH₃ (X);

n = 1-7;
 m = 2-25;
 n₁ = 1-6;
 p = 2-8;
 R, R₁, R₂ = lower alkyl;
 r = 2-25
 X- = a negative ion;
 p₁ = 1-6;
 Y+ = a positive ion
 n₂ = 1-5;
 q = 1-6.

USE - The compositions can be used to treat cancers, tumors,
 malignancies, uncontrolled tissue or cellular proliferation secondary to
 tissue injury, polycystic kidney disease or malaria (claimed). They can be
 used to treat hepatocellular carcinoma, liver metastases, cancers of the
 gastrointestinal tract, pancreas, kidney, colon, cervix, prostate, lung,

leukemia and Kaposi's sarcoma, renal, colon, cervix, prostate or melanoma (claimed).

ADVANTAGE - The taxane-oligomer conjugates exhibit improved solubility characteristics, improved oral bioavailability, and an improved pharmacokinetic profile.

Dwg.0/2

FS CPI

FA AB; GI; DCN

MC CPI: A10-E01; A12-V01; B02-D; B04-C03C; B05-A03B;
B05-C01; B05-C07; B06-A03; B07-D04A; B10-B03B; B10-C04D; B14-A03B;
B14-H01; B14-N10

L74 ANSWER 13 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2001-335427 [35] WPIX

DNC C2001-103552

TI New prodrugs comprising polyethylene glycol units attached to a therapeutic compound by a hydrolyzable bond, useful for the delivery of agents such as etoposide for treating cancer.

DC A25 A96 B02 B07

IN DYAKONOV, T A; EKWURIBE, N N; PRICE, C H;

EKWURIBE, N

PA (NOBE-N) NOBEX CORP; (DYAK-I) DYAKONOV T A; (EKWU-I) EKWURIBE N;
(PRIC-I) PRICE C H

CYC 95

PI WO 2001019406 A2 20010322 (200135)* EN 57 A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000075756 A 20010417 (200140) A61K047-48 <--
EP 1212099 A2 20020612 (200239) EN A61K047-48 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI
NO 2002001213 A 20020513 (200239) A61K000-00
BR 2000013948 A 20020514 (200240) A61K047-48 <--
CZ 2002000928 A3 20020911 (200268) A61K047-48 <--
KR 2002059398 A 20020712 (200306) A61K047-48 <--
JP 2003509385 W 20030311 (200319) 73 A61K047-48 <--
CN 1390143 A 20030108 (200334) A61K047-48 <--
HU 2002004110 A2 20030428 (200337) A61K047-48 <--
ZA 2002002039 A 20030827 (200362) 89 A61K000-00
NZ 517681 A 20040130 (200414) A61K047-48 <--
US 6713454 B1 20040330 (200423) A61K031-704 <--
US 2004180840 A1 20040916 (200461) A61K031-7048 <--

ADT WO 2001019406 A2 WO 2000-US24520 20000907; AU 2000075756 A AU 2000-75756
20000907; EP 1212099 A2 EP 2000-964949 20000907; WO 2000-US24520 20000907;
NO 2002001213 A WO 2000-US24520 20000907; NO 2002-1213 20020312; BR
2000013948 A BR 2000-13948 20000907; WO 2000-US24520 20000907; CZ
2002000928 A3 WO 2000-US24520 20000907; CZ 2002-928 20000907; KR
2002059398 A KR 2002-703276 20020312; JP 2003509385 W WO 2000-US24520
20000907; JP 2001-523037 20000907; CN 1390143 A CN 2000-815508 20000907;
HU 2002004110 A2 WO 2000-US24520 20000907; HU 2002-4110 20000907; ZA
2002002039 A ZA 2002-2039 20020312; NZ 517681 A NZ 2000-517681 20000907;
WO 2000-US24520 20000907; US 6713454 B1 Provisional US 1999-153649P
19990913; US 1999-474915 19991231; US 2004180840 A1 Provisional US
1999-153649P 19990913, Div ex US 1999-474915 19991231, US 2004-808044
20040324

FDT AU 2000075756 A Based on WO 2001019406; EP 1212099 A2 Based on WO
2001019406; BR 2000013948 A Based on WO 2001019406; CZ 2002000928 A3 Based
on WO 2001019406; JP 2003509385 W Based on WO 2001019406; HU 2002004110 A2
Based on WO 2001019406; NZ 517681 A Based on WO 2001019406; US 2004180840
A1 Div ex US 6713454

PRAI US 1999-474915 19991231; US 1999-153649P 19990913;
US 2004-808044 20040324

IC ICM A61K000-00; A61K031-704; A61K031-7048;
A61K047-48

ICS A23L001-30; A61K009-08; A61K009-107; A61K009-14; A61K009-20;
A61K009-48; A61K031-337; A61P035-00; A61P035-02;
A61P035-04; A61P043-00; C07H015-08; C08G063-48

AB WO 200119406 A UPAB: 20010625

NOVELTY - New prodrugs comprising polyethylene glycol units attached to a therapeutic compound by a hydrolyzable bond, useful for the delivery of agents such as etoposide for treating cancer are disclosed.

DETAILED DESCRIPTION - A novel prodrug comprises: (a) at least one

therapeutic compound; and (b) one or more polyethylene glycol (PEG) polymers and/or oligomers, each joined to a bonding site on the therapeutic compound by a hydrolyzable bond, the PEG polymers and/or oligomers each: (i) comprising a straight or branched PEG segment consisting of 2 to 25 PEG units; and (ii) optionally comprising a salt-forming moiety.

An INDEPENDENT CLAIM is also included for a prodrug comprising a therapeutic compound joined by hydrolyzable bond(s) to one or more PEG oligomer(s) selected from formula (II)-(XI): -CO-(CH₂)_n-NR-CH₂CH₂(OC₂H₄)mOCH₃ (II);

-CO-(CH₂)_{n1}-CO-NH-(CH₂)_p-NR-CH₂CH₂(OC₂H₄)mOCH₃ (III);
 -CO-(CH₂)_{n1}-CO-NH-CH₂CH₂(OC₂H₄)_r-NR-CH₂CH₂(OC₂H₄)mOCH₃ (IV);
 -CO-(CH₂)_{n1}-CO-NH-(CH₂)_p-NR-CH₂CH₂(OC₂H₄)mNH₂ (V);
 -CO-(CH₂)_{n1}-CO-NH-(CH₂)_p-NR-CH₂CH₂(OC₂H₄)mNH₃+X- (VI);
 -CO-(CH₂)_{n1}-CO-NH-(CH₂)_p-NR₁-CH₂CH₂(OC₂H₄)mNHR₂ (VII);
 -CO-(CH₂)_{n1}-CO-NH-CH₂CH₂(OC₂H₄)mOCH₂-CO-NH-(CH₂)_pN(CH₃)₂ (VIII);
 -CO-(CH₂)_{n1}(OC₂H₄)mO(CH₂)_{p1}-C(=O)-O-Y+ (IX);
 -CO-(CH₂)_{n2}-NR₁R₂-CH₂CH₂(OC₂H₄)mOCH₃ (X);

n = 1-7;

m = 2-25;

R, R₁, R₂ = lower alkyl

n₁ = 1-6;

p = 2-8;

r = 2-25;

X- = a negative ion;

p₁ = 1-6;

Y+ = a positive ion;

q = 1-5.

USE - The prodrugs can be used for the delivery of drugs such as etoposide. The compositions can be used to treat cancers, tumors or malignancies, e.g. small cell lung cancer, non-small cell lung cancer, testicular cancer, lymphoma, leukemia, ovarian cancer or gastric cancer (claimed).

ADVANTAGE - The prodrugs increase the amphiphilicity of the drugs and facilitate the formation of drugs, the oral delivery of drugs, and the delivery of drugs across the blood brain barrier.

Conjugates of etoposide with PEG was administered intravenously to Sprague-Dawley rats at a dosage of 9 micro mole/kg. Measurement of free etoposide in plasma at various time points demonstrated that peak plasma etoposide concentration was increased by 60% and the half life was extended by approx. 50% in rats given the etoposide conjugate versus rats given etoposide. When the etoposide concentration in brain tissue was measured in these rats the data revealed that injection with the etoposide conjugate led to a 3-fold increase in accumulation of free etoposide in the brain parenchyma. These data agree with other studies demonstrating an increased penetration of the blood-brain barrier by conjugated peptide hormones.

Dwg.0/6

FS

CPI

FA

AB; GI; DCN

MC

CPI: A10-E01; A12-V01; B04-C03C; B06-A02; B06-A03;
 B07-D04A; B10-B03B; B10-C04D; B12-M11; B14-H01

L74 ANSWER 14 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2001-102601 [11] WPIX

DNC C2001-029994

TI New drug-oligomer conjugates facilitate oral delivery of e.g. insulin, and can delay the onset of activity or extend the duration of activity of drug in the bloodstream.

DC A96 B04 C03

IN EKWURIBE, N; RAJAGOPALAN, J; RAMASWAMY, M; EKWURIBE, N N
 ; RAJAGOPALAN, J S

PA (PROT-N) PROTEIN DELIVERY INC; (NOBE-N) NOBEX CORP; (NOBE-N)
 NOBEX INC

CYC 95

PI WO 2000078302 A1 20001228 (200111)* EN 69 A61K031-075 <--
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
 NL OA PT SD SE SL SZ TZ UG ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
 DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
 LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
 SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000057500 A 20010109 (200122)

US 6309633 B1 20011030 (200172)

A61K009-107

NO 2001006143 A 20020218 (200228)

A61K000-00

BR 2000011772 A 20020402 (200231)

A61K031-075 <--

EP 1196157 A1 20020417 (200233) EN A61K031-075 <--
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI

CZ 2001004597 A3 20020515 (200241) A61K031-075 <--
 KR 2002012278 A 20020215 (200257) A61K047-48 <--
 CN 1368877 A 20020911 (200282) A61K031-075 <--
 JP 2003502364 W 20030121 (200308) 68 A61K047-48 <--
 HU 2002003745 A1 20030428 (200337) A61K031-075 <--
 ZA 2001010099 A 20030528 (200341) 80 A61K000-00
 MX 2002000054 A1 20030701 (200366) A61K031-075 <--
 NZ 516109 A 20040430 (200431) A61K031-075 <--

ADT WO 2000078302 A1 WO 2000-US16879 20000619; AU 2000057500 A AU 2000-57500
 20000619; US 6309633 B1 US 1999-336548 19990619; NO 2001006143 A WO
 2000-US16879 20000619, NO 2001-6143 20011217; BR 2000011772 A BR
 2000-11772 20000619, WO 2000-US16879 20000619; EP 1196157 A1 EP
 2000-942956 20000619, WO 2000-US16879 20000619; CZ 2001004597 A3 WO
 2000-US16879 20000619, CZ 2001-4597 20000619; KR 2002012278 A KR
 2001-716204 20011217; CN 1368877 A CN 2000-811540 20000619; JP 2003502364
 W WO 2000-US16879 20000619, JP 2001-504366 20000619; HU 2002003745 A1 WO
 2000-US16879 20000619, HU 2002-3745 20000619; ZA 2001010099 A ZA
 2001-10099 20011207; MX 2002000054 A1 WO 2000-US16879 20000619, MX 2002-54
 20011219; NZ 516109 A NZ 2000-516109 20000619, WO 2000-US16879 20000619

FDT AU 2000057500 A Based on WO 2000078302; BR 2000011772 A Based on WO
 2000078302; EP 1196157 A1 Based on WO 2000078302; CZ 2001004597 A3 Based
 on WO 2000078302; JP 2003502364 W Based on WO 2000078302; HU 2002003745 A1
 Based on WO 2000078302; MX 2002000054 A1 Based on WO 2000078302; NZ 516109
 A Based on WO 2000078302

PRAI US 1999-336548 19990619

IC ICM A61K000-00; A61K009-107; A61K031-075; A61K047-48
 ICS A61K031-13; A61K031-16; A61K031-21;
 A61K031-325; A61K038-00; A61K038-02;
 A61K038-17; A61K038-22; A61K038-28;
 A61K039-385; A61P003-10; C07K001-113

AB WO 200078302 A UPAB: 20010224

NOVELTY - Drug-oligomer conjugates (I) which include a hydrophilic
 component and a lipophilic component linked by a hydrolyzable
 bond, are new.

DETAILED DESCRIPTION - Drug-oligomer conjugates (I), (X), (XI), (XII)
 and (XIII), which include a hydrophilic component and a
 lipophilic component linked by a hydrolyzable bond, are new.

D = therapeutic drug moiety;
 H, H' = hydrophilic moieties selected from straight or
 branched polyethylene glycol (PEG) polymers which have 2-130 ethylene
 glycol subunits and sugars;
 L = lipophilic moiety selected from 2-24C alkyl groups,
 cholesterol and fatty acids;
 m + n + p = at least one, but does not exceed the total number of
 covalent bonding sites on D for the substituents H', L and H-L;
 o (defined in the disclosure) = 1 to the maximum number of covalent
 binding sites on H; and
 L' (defined in the disclosure) = L.

INDEPENDENT CLAIMS are included for:

- (1) drug-oligomer conjugate of formula (XI), in which the S-L and/or
 S-H bond is hydrolyzable;
- (2) drug-oligomer conjugates of formula (XII), in which the S-H
 and/or S-H' bond is hydrolyzable;
- (3) drug-oligomer conjugates of formula (XIII), in which the H-H'
 bond is hydrolyzable;
- (4) drug-oligomer conjugates of formula (X), in which the H-H' bond
 is hydrolyzable; and
- (5) method of providing to a subject an active drug-PEG conjugate of
 formula (X), in which the H-H' bond is hydrolyzable and the H'L bond is
 not hydrolyzable, D is insulin or a derivative, where (X) has enhanced
 activity compared to unconjugated insulin.

S = spacer group selected from sugars, carbohydrates and glycerol;
 n = 1 to the maximum number of covalent binding sites at which S can
 be attached to H;
 o = 1 to the maximum number of covalent binding sites at which L can
 be attached to S;
 p = 1 to the maximum number of covalent binding sites at which
 ((H-Sn)Lo)p can be attached to D; and
 q = 1 to the maximum number of covalent binding sites at which H'
 can be attached to S.

ACTIVITY - Antidiabetic; virucide; antibacterial.
 MECHANISM OF ACTION - None given.
 USE - The new conjugates can be used in treatment or prevention of

any disorders which can be treated by the therapeutic drug D, including bacterial and viral infections. Drug D is preferably insulin, useful in treatment of diabetes.

ADVANTAGE - The new conjugates contain hydrophilic components, lipophilic components and drug components. These components are variously linked such that, upon hydrolysis of hydrolyzable bonds in the conjugates, an active drug-hydrophile conjugate remains. The oligomers are very suitable for oral delivery, while extending the onset of activity of drug-oligomer conjugate in the blood stream. The lipophilic component is preferably selected such that the drug component is inactive until the hydrolyzable bond is hydrolysed. Amphiphilic modification of insulin improves its lipophilicity and stabilizes it against enzymatic degradation while improving its membrane permeability.

Dwg.0/3

FS CPI

FA AB; GI; DCN

MC CPI: A10-E01; A12-V01; B01-D02; B04-C03C; B04-D01;
B04-J03A; B04-N04; B09-D01; B14-A01; B14-A02; B14-F09; C01-D02;
C04-C03C; C04-D01; C04-J03A;
C04-N04; C09-D01; C14-A01; C14-A02; C14-F09

L74 ANSWER 15 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2000-544632 [50] WPIX

DNC C2000-162252

TI Protecting cells against chemical agents, useful in conjunction with e.g. cytostatic or antiviral agents, by treatment with peptide derived from Bowman-Birk protease inhibitor.

DC B04 B05 D16

IN DITTMANN, K; GUEVEN, N; MAYER, C; RODEMANN, H P

PA (UYTU-N) UNIV TUEBINGEN EBERHARD-KARLS

CYC 23

PI DE 19906108 A1 20000817 (200050)* 15 A61K038-56 <--

WO 2000047217 A2 20000817 (200050) GE A61K038-00 <--

RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

W: AU CA JP US

AU 2000029084 A 20000829 (200062) A61K038-00 <--

EP 1150705 A2 20011107 (200168) GE A61K038-56 <--

R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

EP 1150705 B1 20040526 (200435) GE A61K038-56 <--

R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

DE 50006591 G 20040701 (200443) A61K038-56 <--

ADT DE 19906108 A1 DE 1999-1006108 19990213; WO 2000047217 A2 WO 2000-EP1006

20000208; AU 2000029084 A AU 2000-29084 20000208; EP 1150705 A2 EP

2000-907521 20000208, WO 2000-EP1006 20000208; EP 1150705 B1 EP

2000-907521 20000208, WO 2000-EP1006 20000208; DE 50006591 G DE

2000-00006591 20000208, EP 2000-907521 20000208, WO 2000-EP1006 20000208

FDT AU 2000029084 A Based on WO 2000047217; EP 1150705 A2 Based on WO

2000047217; EP 1150705 B1 Based on WO 2000047217; DE 50006591 G Based on

EP 1150705, Based on WO 2000047217

PRAI DE 1999-19906108 19990213

IC ICM A61K038-00; A61K038-56

ICS A61K047-48; A61K048-00; A61P043-00

ICA C07K014-81; C12N005-10

AB DE 19906108 A UPAB: 20001010

NOVELTY - Protecting cells during in vivo or in vitro treatment with a chemical agent (I) by using at least 1 peptide (II) that is a modified form, and/or optionally modified fragment, of the Bowman-Birk protease inhibitor (BBI), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) similar use of a nucleic acid (III) containing a segment that encodes at least 1 (II); and

(2) a pharmaceutical composition containing (II) or (III) in a sufficient amount to protect cells against cytostatic, immunosuppressant and/or virostatic agents.

ACTIVITY - Cytoprotective. The peptide CALSYPAQC (P1) was incubated, at 80 micro M, with normal human fibroblasts for 16 hours, before treatment of the cells for 1 hour with cis-platin at 1 mu g/ml. The cells were washed, incubated for various times (t) in normal medium, then transferred to serum-containing medium for clonogenic assay. For all values of t, the clonogenic survival rate was higher for cells treated with P1 than for controls, e.g. where t = 6 hours, the rate was about 48% for treated cells and about 28% for controls. A similar test with spontaneously transformed fibroblasts (carrying a mutation in the p53 gene) showed that P1 did not protect transformed cells.

MECHANISM OF ACTION - None given.

USE - (II) are used to protect cells during exposure to cytostatic, virostatic or immunosuppressing agents, either in vivo (e.g. during treatment of tumors) or in vitro, e.g. purging leukemia cells from bone marrow or preparing organs for transplantation. Nucleic acid (III) that encode (II) can be used similarly, either in gene therapy or for in vitro cell transformation or transfection.

ADVANTAGE - (II) protect non-target cells (especially rapidly proliferating cells) against the damaging effects of (I), so side-effects are reduced without adverse effects on activity against target cells. This may allow a higher dose of (I) to be used. (II) retain the (radio)protective effects of complete BBI but, unlike BBI, do not significantly inhibit (chymo)trypsin or other serine proteases, so should not damage the pancreas. Since they are small, (II) penetrate cells and tissues quickly and well, and they are easy to prepare. (II) may be stabilized by alkylation, cyclization etc., and may be attached to a protein to extend their half-life in the blood.

Dwg.0/5

FS CPI

FA AB; DCN

MC CPI: B04-C01B; B04-E03; B04-E04; B04-M01; B14-G02; B14-H01;
D05-H12A; D05-H12D5; D05-H17A

L74 ANSWER 16 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2000-423233 [36] WPIX

DNC C2000-128094

TI Supramolecular complexes comprising therapeutic agent and polydimensional polymer network, e.g. based on cyclodextrin, useful for delivery of therapeutic agents such as DNA.

DC A25 A26 A96 B07 D16

IN DAVIS, M E; GONZALEZ, H; HWANG, S

PA (CALY) CALIFORNIA INST OF TECHNOLOGY

CYC 89

PI WO 2000033885 A1 20000615 (200036)* EN 70 A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS
LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ
TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000021627 A 20000626 (200045) A61K047-48 <--
EP 1133318 A1 20010919 (200155) EN A61K047-48 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI

JP 2002531530 W 20020924 (200278) 71 A61K047-40
ADT WO 2000033885 A1 WO 1999-US28547 19991203; AU 2000021627 A AU 2000-21627
19991203; EP 1133318 A1 EP 1999-965967 19991203; WO 1999-US28547 19991203;
JP 2002531530 W WO 1999-US28547 19991203; JP 2000-586375 19991203
FDT AU 2000021627 A Based on WO 2000033885; EP 1133318 A1 Based on WO
2000033885; JP 2002531530 W Based on WO 2000033885
PRAI US 1999-127856P 19990405; US 1998-110847P 19981204
IC ICM A61K047-40; A61K047-48
ICS A61K031-335; A61K031-70; A61K045-00;
A61K047-32; A61K048-00

AB WO 2000033885 A UPAB: 20000801

NOVELTY - Preparation of a supramolecular complex (I) involves contacting at least one therapeutic agent (A) and at least one polymer (II) to form a composite, and treating (II) in the composite to form (I), consisting of (A) and a polydimensional polymer network.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for (I) obtained by the novel preparation method.

ACTIVITY - Anti-HIV; cytostatic; cardiant; tranquilizer; vulnerary; vasotropic; hemostatic.

MECHANISM OF ACTION - None given.

USE - (I) are useful as delivery vehicles for the administration of (A), which is specifically an antibiotic, steroid, polynucleotide, plasmid, peptide, peptide fragment, small molecule, chelating agent or biologically active macromolecule, especially DNA (claimed). Disorders to be treated include cystic fibrosis, Gaucher's disease, muscular dystrophy, AIDS, cancer (e.g. multiple myeloma, leukemia, melanoma or ovarian carcinoma), cardiovascular conditions, (e.g. progressive heart failure, restenosis or hemophilia) or neurological conditions (e.g. brain trauma). (A) may also be agrochemicals, e.g. fungicides, herbicides or insecticides.

ADVANTAGE - By incorporation in (I), (A) is protected against loss of activity (e.g. due to degradation) and given increased solubility and

bioavailability. A wide range of lipophilic or hydrophilic, synthetic or naturally occurring (A) can be incorporated.

Dwg.0/1

FS CPI

FA AB; DCN

MC CPI: A03-A00A; A05-J07; A08-D01; A12-V01; B04-E01; B04-E03; B04-E08; B04-N04; B11-C01; B12-M05; B14-A02B1; B14-F01; B14-F02D; B14-F04; B14-H01B; B14-J01B4; B14-N17B; D05-H10

L74 ANSWER 17 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2000-256190 [22] WPIX

DNC C2000-078134

TI Amphiphilic drug-oligomer conjugate for delivery of therapeutic agents, used to treat central nervous system disorders, or diagnostic agents across the blood brain barrier.

DC A96 B04 B05

IN ANDERSON, W R; ANSARI, A M; EKWURIBE, N N;

PRICE, C H; RADHAKRISHNAN, B; AUSARI, A M;

ANDERSON, W; RHADAKRISHNAN, B

PA (PROT-N) PROTEIN DELIVERY INC; (NOBE-N) NOBEX CORP; (NOBE-N) NOBEX INC; (ANDE-I) ANDERSON W R; (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (PRIC-I) PRICE C H; (RADH-I) RADHAKRISHNAN B

CYC 83

PI WO 2000009073 A2 20000224 (200022)* EN 75 A61K000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
US UZ VN YU ZW

AU 9956726 A 20000306 (200030)

EP 1105142 A2 20010613 (200134) EN A61K031-705 <--

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI

BR 9914280 A 20011113 (200201) A61K031-704 <--

KR 2001072472 A 20010731 (200209) A61K047-48 <--

CN 1323213 A 20011121 (200218) A61K031-704 <--

JP 2002522463 W 20020723 (200263) 78 A61K047-48 <--

MX 2001001694 A1 20020501 (200368) A61K000-00000

US 6703381 B1 20040309 (200418) A61K031-56 <--

US 2004102381 A1 20040527 (200435) A61K038-23 <--

US 2004110735 A1 20040610 (200438) A61K031-56 <--

AU 772494 B2 20040429 (200457) A61K031-705 <--

ADT WO 2000009073 A2 WO 1999-US18248 19990812; AU 9956726 A AU 1999-56726 19990812; EP 1105142 A2 EP 1999-943676 19990812; WO 1999-US18248 19990812; BR 9914280 A BR 1999-14280 19990812; WO 1999-US18248 19990812; KR 2001072472 A KR 2001-701888 20010213; CN 1323213 A CN 1999-812133 19990812; JP 2002522463 W WO 1999-US18248 19990812; JP 2000-564577 19990812; MX 2001001694 A1 WO 1999-US18248 19990812; MX 2001-1694 20010213; US 6703381 B1 US 1998-134803 19980814; US 2004102381 A1 Div ex US 1998-134803 19980814, US 2003-716578 20031119; US 2004110735 A1 Div ex US 1998-134803 19980814, US 2003-716975 20031119; AU 772494 B2 AU 1999-56726 19990812

FDT AU 9956726 A Based on WO 2000009073; EP 1105142 A2 Based on WO 2000009073; BR 9914280 A Based on WO 2000009073; JP 2002522463 W Based on WO 2000009073; MX 2001001694 A1 Based on WO 2000009073; US 2004102381 A1 Div ex US 6703381; US 2004110735 A1 Div ex US 6703381; AU 772494 B2 Previous Publ. AU 9956726, Based on WO 2000009073

PRAI US 1998-134803 19980814; US 2003-716578 20031119;
US 2003-716975 20031119

IC ICM A61K000-00; A61K000-00000; A61K031-56; A61K031-704
; A61K031-705; A61K038-23; A61K047-48

ICS A61K038-00; A61K038-04; A61K038-11;
A61K038-21; A61K038-22; A61K038-26;
A61K038-27; A61K038-33; A61K038-36;
A61K038-42; A61K038-46; A61K038-48;
A61K039-395; A61K045-00; A61P005-02; A61P005-10;
A61P005-14; A61P005-18; A61P029-00; A61P043-00; C07K014-70;
C07K017-00

AB WO 2000009073 A UPAB: 20000508

NOVELTY - Amphiphilic drug-oligomer conjugate comprising a therapeutic compound conjugated to an oligomer comprising a lipophilic moiety coupled to a hydrophilic moiety, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an amphiphilic oligomer-enkephalin conjugate selected from the group consisting of DHA Met-enkephalin-Lys, linoleic Met-enkephalin-Lys, cetyl Met-enkephalin-Lys, cholesterol Met-enkephalin-Lys, palmitate-teg Met-enkephalin-Lys, and di-palmitate-teg Met-enkephalin-Lys;

(2) an amphiphilic oligomer-enkephalin conjugate where the oligomer comprises a lipophile coupled to a hydrophile by a hydrolyzable bond, the conjugate being DHA Met-enkephalin-Lys, linoleic Met-enkephalin-Lys or cetyl Met-enkephalin-Lys;

(3) an amphiphilic oligomer-enkephalin conjugate where the oligomer comprises a lipophile coupled to a hydrophile by a non-hydrolyzable bond, the conjugate being cholesterol Met-enkephalin-Lys, palmitate-teg Met-enkephalin-Lys or di-palmitate-teg Met-enkephalin-Lys;

(4) a method for activating a receptor comprising bringing the receptor into contact with the novel conjugate;

(5) a method for delivering a therapeutic compound across the blood-brain barrier comprising administering the novel conjugate;

(6) a method for inducing analgesia in a subject, comprising administering the novel conjugate; and

(7) a method for altering the binding affinity of a peptide or protein to its receptor, comprising conjugating the peptide to the novel conjugate.

ACTIVITY - Cerebroprotective.

MECHANISM OF ACTION - None given.

USE - The conjugates are capable of traversing the blood-brain barrier and so delivering therapeutic agents used in the treatment of disease states associated with the central nervous system (CNS) or for delivering diagnostic agents across the blood brain barrier.

ADVANTAGE - The conjugates are stable in the bloodstream and resist degradation by the enzymes of the blood brain barrier and in the CNS. The conjugates readily cross the blood brain barrier.

Dwg. 0/10

FS CPI

FA AB; DCN

MC CPI: A12-V01; B01-D02; B04-C01B; B12-K04; B14-J01

L74 ANSWER 18 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 1999-469300 [39] WPIX

DNC C1999-137742

TI Agent for transfer of nucleic acid containing cationic hydrophilic and lipophilic regions, e.g. for gene therapy.

DC A96 B04 B05 D16

IN BYK, G; DUBERTRET, C; PITARD, B; SCHERMAN, D

PA (RHON) RHONE-POULENC RORER SA; (AVET) AVENTIS PHARMA SA

CYC 77

PI WO 9938821 A2 19990805 (199939)* FR 51 C07C000-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL

OA PT SD SE SZ UG ZW

W: AL AT BA BB BG BR CA CN CU CZ EE GD GE HU ID IL IN IS JP KP KR LC

LK LR LT LV MG MK MN MX NO NZ PL RO RU SG SI SK SL TR TT UA US UZ

VN YU

FR 2774394 A1 19990806 (199939) C12N015-88

ZA 9900694 A 19991027 (199951) 75 C08L000-00

NO 2000003880 A 20000728 (200056) C07C000-00

EP 1049793 A2 20001108 (200062) FR C12N015-87

R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU NL PT SE SI

CZ 2000002713 A3 20001115 (200064) C12N015-87

AU 2000043843 A 20010405 (200125) C07C019-00

BR 9907269 A 20010403 (200128) C12N015-87

CN 1289371 A 20010328 (200140) C12N015-87

HU 2001001393 A2 20010828 (200157) C12N015-87

JP 2002501762 W 20020122 (200211) 61 C12N015-09

KR 2001081924 A 20010829 (200215) C12N015-87

MX 2000007036 A1 20011201 (200282) A61K048-00

US 6521252 B1 20030218 (200317) A61K009-127

AU 759197 B 20030410 (200337) C07C019-00

ADT WO 9938821 A2 WO 1999-FR162 19990128; FR 2774394 A1 FR 1998-1065 19980130;

ZA 9900694 A ZA 1999-694 19990128; NO 2000003880 A WO 1999-FR162 19990128;

NO 2000-3880 20000728; EP 1049793 A2 EP 1999-901639 19990128, WO

1999-FR162 19990128; CZ 2000002713 A3 WO 1999-FR162 19990128, CZ 2000-2713

19990128; AU 2000043843 A AU 2000-43843 20000704; BR 9907269 A BR

1999-7269 19990128, WO 1999-FR162 19990128; CN 1289371 A CN 1999-802464

19990128; HU 2001001393 A2 WO 1999-FR162 19990128, HU 2001-1393 19990128;

JP 2002501762 W WO 1999-FR162 19990128, JP 2000-530060 19990128; KR

2001081924 A KR 2000-708257 20000728; MX 2000007036 A1 MX 2000-7036

20000718; US 6521252 B1 Provisional US 1998-77026P 19980306, Cont of WO

1999-FR162 19990128, US 2000-610727 20000706; AU 759197 B AU 2000-43843

20000704

FDT EP 1049793 A2 Based on WO 9938821; CZ 2000002713 A3 Based on WO 9938821;
BR 9907269 A Based on WO 9938821; HU 2001001393 A2 Based on WO 9938821; JP
2002501762 W Based on WO 9938821; AU 759197 B Previous Publ. AU 2000043843

PRAI US 1998-77026P 19980306; FR 1998-1065 19980130

IC ICM A61K009-127; A61K048-00; C07C000-00; C07C019-00; C08L000-00;
C12N015-09; C12N015-87; C12N015-88

ICS A61K031-7105; A61K031-711; A61K038-05;
A61K047-48; A61P043-00; C07C323-60; C07K005-062

AB WO 9938821 A UPAB: 19990928

NOVELTY - Agent (I) for transfer of nucleic acid (II) comprises:
(a) at least one cationic hydrophilic region that can
associate non-covalently with (II); and
(b) at least one lipophilic region.
These regions are linked by a spacer arm that also includes at least
one disulfide bridge such that reduction causes:
(a) partial degradation of the lipophilic region; or
(b) splitting of (I) into two where this is symmetrical.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the
following:
(1) composition containing (I) and at least one (II); and
(2) preparation of the compositions of (1).
ACTIVITY - None given.
MECHANISM OF ACTION - None given.
USE - (I) are used to deliver (II) to cells, in vitro, in vivo or ex
vivo, e.g. for production of recombinant proteins, to screen for
regulators of gene expression, for cloning, to produce transgenic animals,
for vaccination, for gene therapy, for immunotherapy etc.
ADVANTAGE - The hydrophilic part of (I) provides efficient
complexation with (I) and the lipophilic part renders this ionic
interaction insensitive to the external medium, by covering the particle
formed with a lipid layer. When the disulfide bond is reduced, a
detergent, able to destabilize membranes, is generated, so a greater
quantity of nucleic acid can be transported to the transcriptional
machinery of the host cell. (I) have an inherently low toxicity, provide
efficient transfer (and are thus required only in small amounts) and
increase serum resistance.
Dwg.0/9

FS CPI

FA AB; DCN

MC CPI: A12-V01; B01-D02; B04-E01; B10-A04; B10-B01B; B12-K04F;
B14-S03; B14-S11; D05-H07; D05-H09; D05-H12E; D05-H16A; D05-H17B.

L74 ANSWER 19 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 1997-549493 [50] WPIX

CR 1998-427687 [36]

DNC C1997-175210

TI Polypeptide composition able to reversibly transit between
lipophilic and hydrophilic forms - is useful for
transporting compounds across lipid layers.

DC B04 B07

IN SUMMERTON, J E; WELLER, D D

PA (ANTI-N) ANTIVIRALS INC; (AVIB-N) AVI BIOPHARMA INC

CYC 76

PI WO 9740854 A2 19971106 (199750)* EN 73 A61K047-48 <--
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT
SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE GH
HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX
NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN YU
AU 9729298 A 19971119 (199812)
EP 966303 A2 19991229 (200005) EN
R: AT BE CH DE FR GB IT LI LU NL
US 6030941 A 20000229 (200018) A01N037-18
JP 2000509394 W 20000725 (200041) 93 A61K047-48 <--
AU 729643 B 20010208 (200113) A61K047-48 <--

ADT WO 9740854 A2 WO 1997-US7335 19970430; AU 9729298 A AU 1997-29298
19970430; EP 966303 A2 EP 1997-923513 19970430, WO 1997-US7335 19970430;
US 6030941 A Provisional US 1996-16347P 19960501, Provisional US
1996-28609P 19961023, US 1997-848844 19970430; JP 2000509394 W JP
1997-539221 19970430, WO 1997-US7335 19970430; AU 729643 B AU 1997-29298
19970430

FDT AU 9729298 A Based on WO 9740854; EP 966303 A2 Based on WO 9740854; JP
2000509394 W Based on WO 9740854; AU 729643 B Previous Publ. AU 9729298,
Based on WO 9740854

PRAI US 1996-28609P 19961023; US 1996-16347P 19960501;

ICA C07D307-20

AB WO 9704796 A UPAB: 20040310

Compsn., comprising a therapeutic agent, coupled conjugatively, covalently, and stabilisingly with molecule(s) of a non-naturally occurring polymer (NNOP), which contains hydrophilic and lipophilic (H and L) parts and which imparts balanced H and L characteristics to the compsn., so that it is soluble in solvents and able to interact with biological membranes, is new.

USE - The conjugate is of use for admin. of a wide range of diagnostic, prophylactic, and therapeutic agents, partic. those degraded by plasma proteases when admin. parenterally, or gastrointestinal proteases on oral admin. These include proteins, enzymes, peptides, nucleosides, nucleotides, antiviral or antineoplastic agents, antibiotics, antiarrhythmics, and anticoagulants.

Most notably, the conjugate is with insulin; other examples are calcitonin, ACTH, glucagon, somatostatin, somatotropin, somatomedin, thyroid stimulating or parathyroid hormone, erythropoietin, hypothalamic releasing factor, prolactin, endorphins, antibodies, haemoglobin, soluble CD-4, clotting factors, tissue plasminogen activator, enkephalins, vasopressin, non-natural opioids, superoxidedismutase, interferon, asparaginase, arginase, arginine deaminase or adenosine deaminase, ribonuclease, trypsin, chymotrypsin, papain, polypeptides, enzyme-protein or antibody-hapten conjugates, viral epitopes; antivirals are arabino-furanosyl-adenine, acylguanosine, nordeoxy-guanosine, AZT, ddA, ddC; anticancer agents are ddI, floxuridine, 6-mercaptopurine, doxorubicin, daunorubicin, and L-darubicin; antibiotics are erythromycin, vancomycin, oleandomycin, and ampicillin; antiarrhythmics are quinidine; and as an anticoagulant, heparin.

Examples of diagnostic use are in screening for AIDS, hepatitis, or rubella, or other immunoassay. Both clinical and veterinary applications are envisaged.

The conjugates may also have applications in prophylaxis or treatment of plant disorders, with insecticidal, herbicidal, fungicidal, and/or pesticidal active agents.

ADVANTAGE - The conformation of the conjugate can be arranged to impart increased resistance to enzymatic degradation to the bioactive drug, notably by the lipophilic moiety being on the exterior, when viewed in 3-dimensional form, providing protection. Linkage of the active agent can be through a divalent spacer gp., e.g., polyethylene glycol, so as to avoid reduction of activity caused by a direct link. The polymer may also improve thermal and room temperature stability, improving shelf life and robustness of agent packs and kits. Polyalkylene glycol and polysorbate derivs., partic with M.weight in the pref. range of 500-10000 D, have no antigenic or immunogenic response, high biocompatibility, and ease of excretion.

Dwg.0/2

FS CPI

FA AB; DCN

MC CPI: A10-E07; A10-E08A; A12-V01; A12-V03C2; B04-C03; B04-C03C; B04-J03A; B11-C08E; B12-K04A4

L74 ANSWER 21 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 1994-341060 [42] WPIX

CR 1995-274901 [36]; 1997-145369 [13]; 2001-373408 [39]; 2004-178651 [17]; 2004-178652 [17]

DNC C1994-155400

TI New peptide-polymer conjugates - containing polymer with lipophilic and hydrophilic components, especially polyethylene glycol derivative.

DC A96 B04

IN EKWURIBE, N N

PA (PROT-N) PROTEIN DELIVERY INC; (NOBE-N) NOBEX CORP

CYC 24

PI US 5359030 A 19941025 (199442)* 22 C07K007-40 <--

WO 9426778 A1 19941124 (199501) EN 76

RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE

W: AU CA JP

AU 9469466 A 19941212 (199522)

EP 707596 A1 19960424 (199621) EN

R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

JP 08510255 W 19961029 (199705) 81 C07K014-00 <--

CN 1120457 A 19960417 (199745)# A61K038-22 <--

EP 707596 A4 19971112 (199840)

AU 694919 B 19980806 (199843)

IL 109619 A 20001206 (200103) A61K038-17 <--

MX 196965 B 20000615 (200133)# C07K007-040 <--

EP 1264837 A1 20021211 (200301) EN C07K001-107 <--

US 1997-848844 19970430
 IC ICM A01N037-18; A61K047-48
 ICS A61K031-337; A61K031-74; A61P001-04; A61P031-04;
 A61P035-00; A61P043-00
 ICA A61K038-00
 AB WO 9740854 A UPAB: 20010307
 A new composition, for transporting a compound from a low pH environment across a lipid layer to a higher pH aqueous compartment, comprises: (a) a polypeptide (PP) containing one or more pairs of carboxyl groups; where: (i) the carboxyl groups of a pair are separated by 0, 2 or 3 amino acids; (ii) the PP has a length of 8-100 amino acid residues; (iii) the PP can undergo a reversible transition between a lipophilic form (which can partition from the low pH environment into the lipid layer) and a hydrophilic form (which can partition preferentially from the lipid layer into the higher pH compartment; and (iv) the PP contains an initiator moiety at one end region, to facilitate entry of the end region into the lipid layer; where the PP is able to traverse the lipid layer from the low-pH to the higher-pH compartment; and (b) the compound to be transported, which is covalently attached to the PP.
 USE - The composition may be used for delivery of drugs across membranes (especially cell membranes or the extracellular lipid matrix of the stratum corneum) for treatment of, e.g., tumours, Helicobacter pylori infection, tooth decay (where the cell is an acid-producing cariogenic bacterial cell). The composition may be administered orally, transdermally or parenterally.
 ADVANTAGE - The compositions allow more effective delivery of drugs and other compounds across lipid layers. They can deliver compounds into cells via a route which avoids exposure to lysosomal enzymes. The compositions may be prepared using known methods.
 Dwg.0/14
 FS CPI
 FA AB; DCN
 MC CPI: B04-C01G; B04-N04

L74 ANSWER 20 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
 AN 1997-145369 [13] WPIX
 CR 1994-341060 [42]; 1995-274901 [36]; 2001-373408 [39]; 2004-178651 [17];
 2004-178652 [17]
 DNC C1997-046381
 TI Bioactive agent conjugates with hydrophilic or lipophilic polymers - having improved stability to degradation and passage through membranes, used with proteins, peptide(s), e.g., insulin, nucleotide(s), antibiotics, etc..
 DC A25 A96 B04 B07
 IN EKWURIBE, N N
 PA (PROT-N) PROTEIN DELIVERY INC
 CYC 25
 PI WO 9704796 A1 19970213 (199713)* EN 60 A61K038-16 <--
 RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
 W: AU CA CN IL JP MX
 AU 9666409 A 19970226 (199725)
 US 5681811 A 19971028 (199749) 23 A61K037-16
 EP 841936 A1 19980520 (199824) EN
 R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
 AU 698944 B 19981112 (199906)
 JP 11511131 W 19990928 (199952) 60 A61K047-48 <--
 MX 9800883 A1 19980901 (200017)
 CN 1192690 A 19980909 (200040) A61K038-16 <--
 MX 205730 B 20011219 (200362) A61K038-16 <--
 ADT WO 9704796 A1 WO 1996-US12425 19960729; AU 9666409 A AU 1996-66409 19960729; US 5681811 A Div ex US 1993-59701 19930510, CIP of US 1994-276890 19940719, US 1995-509422 19950731; EP 841936 A1 EP 1996-926169 19960729, WO 1996-US12425 19960729; AU 698944 B AU 1996-66409 19960729; JP 11511131 W WO 1996-US12425 19960729, JP 1997-507838 19960729; MX 9800883 A1 MX 1998-883 19980130; CN 1192690 A CN 1996-196079 19960729; MX 205730 B WO 1996-US12425 19960729, MX 1998-883 19980130
 FDT AU 9666409 A Based on WO 9704796; US 5681811 A Div ex US 5359030, CIP of US 5438040; EP 841936 A1 Based on WO 9704796; AU 698944 B Previous Publ. AU 9666409, Based on WO 9704796; JP 11511131 W Based on WO 9704796
 PRAI US 1995-509422 19950731; US 1993-59701 19930510;
 US 1994-276890 19940719
 REP US 4003792; US 4179337; US 4585754
 IC ICM A61K037-16; A61K038-16; A61K047-48
 ICS A61K031-47; A61K031-52; A61K031-55;
 A61K031-70; A61K031-715; A61K038-00;
 A61K038-28; A61K049-00; C08L059-00

DE 69325279 E 19990715 (199934) C07K007-06 <--
 ES 2136130 T3 19991116 (200001) C07K007-06 <--
 ADT WO 9406450 A1 WO 1993-US9057 19930917; AU 9351379 A AU 1993-51379
 19930917; EP 661986 A1 EP 1993-922358 19930917, WO 1993-US9057 19930917;
 US 5624894 A Cont of US 1992-946062 19920917, US 1995-428488 19950427; EP
 661986 A4 EP 1993-922358 ; AU 694094 B AU 1993-51379 19930917; EP
 661986 B1 EP 1993-922358 19930917, WO 1993-US9057 19930917; DE 69325279 E
 DE 1993-625279 19930917, EP 1993-922358 19930917, WO 1993-US9057 19930917;
 ES 2136130 T3 EP 1993-922358 19930917
 FDT AU 9351379 A Based on WO 9406450; EP 661986 A1 Based on WO 9406450; AU
 694094 B Previous Publ. AU 9351379, Based on WO 9406450; EP 661986 B1
 Based on WO 9406450; DE 69325279 E Based on EP 661986, Based on WO
 9406450; ES 2136130 T3 Based on EP 661986
 PRAI US 1992-946062 19920917; US 1995-428488 19950427
 REP US 4888427; US 4829070
 IC ICM A61K037-00; A61K038-03; C07K005-02;
 C07K007-06
 ICS A61K038-02; A61K047-48; C07K005-08;
 C07K005-10; C07K007-02; C07K014-70
 AB WO 9406450 A UPAB: 19981021
 Dihydropyridine substd. peptides of formula (I), and their
 pharmaceutically acceptable salts, and the corresponding pyridinium salts
 (II) are new. In the formula, Z = direct bond or 1-6C alkylene, attached
 to ring C or N; R1 = 1-7C (halo)alkyl or 7-12C aralkyl when Z is attached
 to C or a bond when Z is attached to N; R2 and R3 = H, halo, CN, 1-7C
 alkyl, alkoxy or alkyl S(O)n (n=0-2), 2-8C alkoxycarbonyl or alkanoyloxy,
 1-7C haloalkyl, CH=NOR''' or CONR'R''; R', R'' and R''' = H or 1-7C alkyl;
 one of R2 and R3, together with an adjacent ring C may form a fused
 benzene ring, opt. substd. by 1 or 2 substituents as defined for R2 and R3,
 or opt. protected OH; the dotted lines indicate 1,4- or
 1,6-dihydropyridine, 1,4- or 1,2-dihydroquinoline or 1,2-
 dihydroisoquinoline; spacer indicates 1-3L amino acid residues, the
 N-terminal one being bonded to CO; peptide indicates a pharmacologically
 active peptide of 2-20 amino acids, the N-terminal one being bonded to the
 C terminus of spacer, and the C-terminal one having esterified function
 COOR4; R4 = 5-22C alkyl or alkenyl, or 6-30C polycycloalkyl-CpH2p or
 polycycloalkenyl-CpH2p; p = 0-3; X = anion of nontoxic, pharmaceutically
 acceptable acid.
 USE - (I) are used for site specific and/or sustained delivery of
 active peptides to the brain. Because they are lipophilic they
 can cross the blood-brain barrier, but once in the brain they are oxidised
 to hydrophilic (II) which is unable to leave the brain. Brain
 enzymes then degrade (II), releasing the active peptide. (II) are also
 intermediates in synthesis of (I). Pref. peptides are the analgesic
 kyotrophin (Tyr-Arg) which stimulates release of enkephalins;
 thyrotropin-releasing hormone or its analogues, or Met5- and
 Leu5-enkephalins or their analogues which are analgesics and affect memory
 so can be used to treat e.g. Alzheimer's disease).
 Dwg.1/5
 FS CPI
 FA AB; GI; DCN
 MC CPI: B04-C01; B04-N02; B06-D02; B06-D03; B07-D04A; B07-D04C

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FILE COVERS 1907 - 13 Oct 2004 VOL 141 ISS 16
 FILE LAST UPDATED: 12 Oct 2004 (20041012/ED)

This file contains CAS Registry Numbers for easy and accurate

Searched by Noble Jarrell

R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
 JP 2003160598 A 20030603 (200346) 27 C07K014-62 <--
 JP 2003206236 A 20030722 (200351) 32 A61K038-00 <--
 ADT US 5359030 A US 1993-59701 19930510; WO 9426778 A1 WO 1994-US5204
 19940510; AU 9469466 A AU 1994-69466 19940510; EP 707596 A1 EP 1994-917946
 19940510, WO 1994-US5204 19940510; JP 08510255 W JP 1994-525657 19940510,
 WO 1994-US5204 19940510; CN 1120457 A CN 1994-117233 19941014; EP 707596
 A4 EP 1994-917946 19940510; AU 694919 B AU 1994-69466 19940510; IL 109619
 A IL 1994-109619 19940511; MX 196965 B MX 1994-7611 19940930; EP 1264837
 A1 Div ex EP 1994-917946 19940510, EP 2002-77075 19940510; JP 2003160598 A
 Div ex JP 1994-525657 19940510, JP 2002-260459 19940510; JP 2003206236 A
 Div ex JP 1994-525657 19940510, JP 2002-260460 19940510
 FDT AU 9469466 A Based on WO 9426778; EP 707596 A1 Based on WO 9426778; JP
 08510255 W Based on WO 9426778; AU 694919 B Previous Publ. AU 9469466,
 Based on WO 9426778; EP 1264837 A1 Div ex EP 707596
 PRAI US 1993-59701 19930510; CN 1994-117233 19941014;
 MX 1994-7611 19940930
 REP 02Jnl.Ref; US 4044196; US 4849405; US 5013556; 1.Jnl.Ref; EP 354855; EP
 92918; US 4179337; US 5108568
 IC ICM A61K038-00; A61K038-17; A61K038-22;
 C07K001-107; C07K007-040; C07K007-40;
 C07K014-00; C07K014-62
 ICS A61K038-02; A61K038-04; A61K038-11;
 A61K038-21; A61K038-23; A61K038-26;
 A61K038-27; A61K038-28; A61K038-35;
 A61K038-43; A61K038-44; A61K038-46;
 A61K038-48; A61K047-34; A61K047-48; A61P003-10;
 A61P005-50; C07K007-036; C07K007-36;
 C07K017-008; C07K017-02; C07K017-08;
 C08G065-26; C08G069-10; C08G069-40; C08G081-02; C08H001-00;
 C08H001-000; C08L071-02
 AB US 5359030 A UPAB: 20040310
 New conjugates comprise: (a) a peptide (I) covalently coupled to one or
 more mols. of a non-natural polymer having lipophilic and
 hydrophilic polymer components, where the conjugate is soluble in
 pharmaceutically acceptable solvents and is able to interact with
 biological membranes.
 Pref. conjugate (II) comprises a physiologically active peptide
 covalently coupled to one or more mols. of a polymer comprising a linear
 polyalkylene glycol component and a lipophilic component
 arranged so as to enhance the resistance of the peptide to enzymatic
 degradation in vivo; the peptide is soluble in aqueous solvents and is active
 against plant disorders.
 USE - The conjugates may be used for therapeutic or diagnostic
 purposes.
 ADVANTAGE - The conjugates have improved properties compared with the
 free peptide, e.g. better epithelial penetration, resistance to
 proteolytic degradation, affinity for endogenous transport systems and/or
 resistance to stomach acidity.
 Dwg.0/2
 FS CPI
 FA AB; GI; DCN
 MC CPI: A12-V01; A12-V03C2; B04-C01; B04-C03C;
 B12-K04; B14-E01
 L74 ANSWER 22 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
 AN 1994-118149 [14] WPIX
 DNC C1994-054638
 TI New peptide derivs. with di hydro pyridine redox gp. - for site specific
 and sustained drug delivery to the brain.
 DC B04
 IN BODOR, N S
 PA (UYFL) UNIV FLORIDA
 CYC 46
 PI WO 9406450 A1 19940331 (199414)* EN 271 A61K037-00
 RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE
 W: AT AU BB BG BR BY CA CH CZ DE DK ES FI GB HU JP KP KR KZ LK LU LV
 MG MN MW NL NO NZ PL PT RO RU SD SE SK UA VN
 AU 9351379 A 19940412 (199431) A61K037-00
 EP 661986 A1 19950712 (199532) EN A61K037-00
 R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
 US 5624894 A 19970429 (199723) 101 A61K038-03 <--
 EP 661986 A4 19970423 (199735) A61K037-00
 AU 694094 B 19980716 (199840) C07K005-02 <--
 EP 661986 B1 19990609 (199927) EN C07K007-06 <--
 R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

substance identification.

=> d all 164 tot

L64 . ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN
 AN 2001:131193 HCAPLUS
 DN 134:183490
 ED Entered STN: 22 Feb 2001
 TI Hydrophilic and lipophilic balanced microemulsion formulations of
 free-form and/or conjugation-stabilized therapeutic agents such as insulin
 IN Ekwuribe, Nnochiri Nkem; Ramaswamy, Muthukumar;
 Radhakrishnan, Balasingam; Allaudeen, Hameedsulthan S.
 PA Protein Delivery, Inc., USA
 SO U.S., 32 pp., Cont.-in-part of U. S. 5,681,811.
 CODEN: USXXAM
 DT Patent
 LA English
 IC ICM A61K038-38
 ICS C07K014-62
 NCL 514003000
 CC 63-6 (Pharmaceuticals)
 Section cross-reference(s): 1, 2
 FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6191105	B1	20010220	US 1997-958383	19971027
	US 5359030	A	19941025	US 1993-59701	19930510
	US 5438040	A	19950801	US 1994-276890	19940719
	US 5681811	A	19971028	US 1995-509422	19950731
	US 2003229006	A1	20031211	US 2003-448524	20030530
	US 2003229010	A1	20031211	US 2003-448535	20030602
PRAI	US 1993-59701	A3	19930510		
	US 1994-276890	A2	19940719		
	US 1995-509422	A2	19950731		
	US 1997-958383	A3	19971027		
	US 2000-614203	A1	20000712		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 6191105	ICM ICS NCL	A61K038-38 C07K014-62 514003000
US 5359030	ECLA	A61K009/107D; A61K047/48H4P; A61K047/48K; A61K049/00P4F; C07K001/107D4; C07K014/62; C12N009/96
US 5438040	ECLA	A61K009/107D; A61K047/48H4P; A61K047/48K; A61K049/00P4F; C07K001/107D4; C07K014/62; C12N009/96
US 5681811	ECLA	A61K009/107D; A61K047/48H4P; A61K047/48K; A61K049/00P4F; C07K001/107D4; C07K014/62
US 2003229006	ECLA	A61K009/107D; A61K047/48K; A61K049/00P4F; C07K001/107D4; C07K014/62; A61K038/28; A61K038/46; A61K047/4H4P; C12N009/96
US 2003229010	ECLA	A61K009/107D; A61K038/28; A61K047/48H4P; A61K047/48K; A61K049/00P4F; C07K001/107D4; C07K001/62; C12N009/96

AB A therapeutic formulation comprising a microemulsion of a therapeutic agent in free and/or conjugate coupled form, wherein the microemulsion comprises a water-in-oil (w/o) microemulsion including a lipophilic phase and a hydrophilic phase, and has a hydrophilic and lipophilic balance (HLB) value between 3 and 7 is described. The therapeutic agent is selected from the group consisting of insulin, calcitonin, ACTH, glucagon, somatostatin, somatotropin, somatomedin, parathyroid hormone, erythropoietin, hypothalamic releasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins, vasopressin, non-naturally occurring opioids, superoxide dismutase, interferon, asparaginase, arginase, arginine deaminase, adenosine deaminase, RNase, trypsin, chymotrypsin, papain, Ara-A (Arabinofuranosyladenine), acylguanosine, nordeoxyguanosine, azidothymidine, dideoxyadenosine, dideoxycytidine, dideoxyinosine, floxuridine, 6-mercaptopurine, doxorubicin, daunorubicin, or I-darubicin, erythromycin, vancomycin, oleandomycin, ampicillin, quinidine and heparin. In a particular aspect, the invention comprises an insulin composition suitable for parenteral as well as non-parenteral administration, preferably oral or parenteral administration, comprising insulin covalently coupled with a polymer including (i) a linear polyalkylene glycol moiety and (ii) a lipophilic moiety, wherein the insulin, the linear polyalkylene glycol moiety and the lipophilic moiety

- are conformationally arranged in relation to one another such that the insulin in the composition has an enhanced in vivo resistance to enzymic degradation, relative to insulin alone. The microemulsion compns. of the invention are usefully employed in therapeutic as well as non-therapeutic, e.g., diagnostic, applications. For example, a microemulsion formulation was prepared containing Capmul MCM 53.0, Centrophase 31 5.7, propylene glycol 19.9, Tween 80 1.4, hexyl insulin in NaP buffer 15 mg/mL, and NaP buffer up to 100%, resp. Also, preparation of hexyl insulin conjugates with Me (ethylene glycol)7-O-hexanoic acid was carried out.
- ST drug conjugate microemulsion stabilization; insulin conjugate microemulsion stabilization
- IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-10, esters with propylene glycol; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT Diagnosis
(agents; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT Polyoxyalkylenes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates with tetrahydropyran derivative and insulin; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT Antidiabetic agents
Hydrophile-lipophile balance value
(hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT Diglycerides
Enkephalins
Glycerides, biological studies
Hypothalamic hormones
Interferons
Lecithins
Monoglycerides
Opioids
Polymers, biological studies
Polyoxyalkylenes, biological studies
Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT Drug delivery systems
(microemulsions; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT Surfactants
(nonionic; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT Drug delivery systems
(oral; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT Drug delivery systems
(parenterals; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT Alcohols, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyhydric; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vegetable; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT 24167-76-8, Sodium phosphide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(buffer; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT 102-82-9, Tri-n-butylamine 3344-77-2, 12-Bromo-1-dodecanol 7075-11-8
7693-46-1, p-Nitrophenylchloroformate 9004-74-4 9005-66-7 9005-70-3
11070-73-8, Bovine insulin 25512-65-6, Dihydropyran 161489-28-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)
- IT 7075-11-8DP, tri-Bu derivative 88517-92-4P 100601-63-6P 161756-38-3P
161756-39-4P 212969-35-2P 326892-08-4P 326892-09-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)

IT 9004-95-9DP, Polyoxyethylene cetyl ether, conjugates with tri-Bu AraCMP
 9004-99-3DP, Polyethylene glycol monostearate, conjugates with insulin
 9005-66-7DP, conjugates with insulin 9005-70-3DP, conjugates with polysorbate trioleate 11070-73-8DP, Bovine insulin, conjugates 25322-68-3DP, Polyethylene glycol, conjugates with tetrahydropyran derivative and insulin 88517-92-4DP, conjugates with insulin and polyethylene glycol 212969-35-2DP, conjugates with hexyl insulin

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)

IT 50-44-2, 6-Mercaptopurine 50-91-9, Floxuridine 56-54-2, Quinidine 57-55-6, Propylene glycol, biological studies 57-55-6D, Propylene glycol, esters 69-53-4, Ampicillin 69-65-8, D-Mannitol 114-07-8, Erythromycin 118-00-3D, Guanosine, acyl derivs., biological studies 1404-90-6, Vancomycin 1984-06-1, Sodium octanoate 3922-90-5, Oleandomycin 4097-22-7, Dideoxyadenosine 5536-17-4, Ara-A 7481-89-2, Dideoxycytidine 9000-96-8, Arginase 9001-73-4, Papain 9001-99-4, RNase 9002-07-7, Trypsin 9002-60-2, ACTH, biological studies 9002-62-4, Prolactin, biological studies 9002-64-6, Parathyroid hormone 9002-71-5, Thyroid stimulating hormone 9002-72-6, Somatotropin 9004-07-3, Chymotrypsin 9004-10-8, Insulin, biological studies 9004-10-8D, Insulin, conjugates with hexanoic acid derivative, biological studies 9004-10-8D, Insulin, hexyl polymer conjugate, biological studies 9005-49-6, Heparin, biological studies 9005-65-6, Tween 80 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9015-68-3, Asparaginase 9026-93-1, Adenosine deaminase 9027-98-9 9038-70-4, Somatomedin 9054-89-1, Superoxide dismutase 11000-17-2, Vasopressin 11096-26-7, Erythropoietin 20830-81-3, Daunorubicin 23214-92-8, Doxorubicin 25322-68-3, Polyethylene glycol 30516-87-1, Azidothymidine 51110-01-1, Somatostatin 58957-92-9, I-Darubicin 60118-07-2, Endorphin 69655-05-6, Dideoxyinosine 82410-32-0 87090-08-2, Labrafil M 1944 120300-18-7, Caprol PGE 860 156259-68-6, Capmul MCM 195739-92-5, Centrophase 31

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)

IT 9001-92-7, Protease
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (inhibitors; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin but not protease inhibitor)

IT 8049-47-6, Pancreatin 9001-75-6, Pepsin
 RL: CAT (Catalyst use); USES (Uses)
 (insulin and its conjugates stability in)

RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD

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=> d all 173 tot

L73 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1985:589177 HCAPLUS
DN 103:189177
ED Entered STN: 14 Dec 1985
TI Plasma and tear concentrations of antibiotics administered parenterally to cattle
AU Punch, P. I.; Costa, N. D.; Chambers, E. D.; Slatte, D. H.; Wilcox, G. E.
CS Sch. Vet. Stud., Murdoch Univ., Murdoch, 6150, Australia
SO Research in Veterinary Science (1985), 39(2), 179-87
CODEN: RVSTA9; ISSN: 0034-5288
DT Journal
LA English
CC 1-2 (Pharmacology)
AB Chloramphenicol [56-75-7], erythromycin [114-07-8], gentamicin [1403-66-3], oxytetracycline [79-57-2], penethamate [3689-73-4], and procaine benzylpenicillin [6130-64-9] were administered parenterally to cattle and the concns. of these antibiotics in plasma and tears were assayed microbiol. Concns. in plasma and tears were correlated for all antibiotics tested but the concentration of antibiotic in tears and the tear flow rate were not correlated. Lipophilic drugs diffused into the tears in higher concns. than did drugs which were not lipophilic. Concns. of lipophilic but not hydrophilic antibiotics in tears could be predicted from the Henderson-Hasselbach equation. In cattle, it is possible through parenteral administration of chloramphenicol, erythromycin, gentamicin, or oxytetracycline to achieve antibiotic concns. in the tears which are bacteriostatic to Moraxella bovis, a primary etiol. agent of infectious bovine keratoconjunctivitis.
ST plasma tear antibiotic cattle
IT Cattle
(antibiotics levels in plasma and tears in, correlation of, keratoconjunctivitis from Moraxella bovis treatment in relation to)
IT Tear
(antibiotics of, levels in plasma correlation with, in cattle)
IT Blood plasma
(antibiotics of, levels in tears correlation with, in cattle)
IT Moraxella bovis
(keratoconjunctivitis from, in cattle, treatment of, antibiotic levels in plasma and tears in relation to)

IT Lipophilicity
(of antibiotics, transport into tears in cattle in relation to)

IT Antibiotics
(of plasma and tears, correlation of, in cattle)

IT Eye, disease or disorder
(keratoconjunctivitis, from Moraxella bovis, treatment of, antibiotic levels in plasma and tears of cattle in relation to)

IT 56-75-7 79-57-2 114-07-8 1403-66-3 3689-73-4
6130-64-9
RL: BIOL (Biological study)
(of plasma and tears, correlation of, in cattle)

L73 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1982:593254 HCAPLUS
DN 97:193254
ED Entered STN: 12 May 1984
TI Critical components of opioid peptides for specific recognition of .mu. and .delta. receptors
AU Gacel, G.; Fournie-Zaluski, M. C.; David, M.; Meunier, J. C.; Morgat, J. L.; Roques, B. P.
CS Dep. Chim. Org., CNRS, Paris, 75006, Fr.
SO Adv. Endog. Exog. Opioids, Proc. Int. Narc. Res. Conf., 12th (1981), 377-9. Editor(s): Takagi, Hiroshi; Simon, Eric J. Publisher: Kodansha, Tokyo, Japan.
CODEN: 48NVAY
DT Conference
LA English
CC 2-2 (Mammalian Hormones)
AB Of the 13 opioid peptides tested for binding in the guinea pig ileum and mouse vas deferens, Tyr-L-Ser-Gly-Phe-Leu-Thr (DSTLE) [75644-90-5] and Tyr-D-Ala-Gly-NHCH(CH₃)CH₂ (TRIMU 4) [72732-17-3] were the most selective probes for use in the characterization of .delta. and .mu. receptor subtypes, resp. DSTLE labeled only .delta. sites in rat brain homogenates, whereas Tyr-D-Ala-Gly-Phe-D-Leu [63631-40-3] bound both .mu. and .delta. receptor subtypes and TRIMU 4 preferentially labeled .mu.-sites. Substitution with 2-D-amino acids, shortening the enkephalin sequence, removal of the 4-phenylalanine residue, and addition of a C-terminal alkyl lipophilic chain enhanced the .mu.-receptor specificity of the enkephalins, whereas lengthening the enkephalin chain, introduction of a 5-leucine residue, and insertion of an hydrophilic residue, such as D-serine, in position 2 enhanced the .delta.-receptor specificity of the enkephalins.
ST enkephalin receptor structure activity; opioid activity enkephalin analog
IT Brain, metabolism
(enkephalin analog binding by, structure in relation to)

IT Enkephalins
RL: PROC (Process)
(opiate receptor binding of, structure in relation to)

IT Molecular structure-biological activity relationship
(opiate receptor-binding, of enkephalin analogs)

IT Receptors
RL: BIOL (Biological study)
(.delta.-, enkephalin binding by, structure in relation to)

IT Receptors
RL: BIOL (Biological study)
(.mu.-, enkephalin binding by, structure in relation to)

IT 58569-55-4 58822-25-6 60117-18-2 63631-40-3
64854-64-4 66609-07-2 72732-16-2 72732-17-3 72732-18-4
75644-90-5 80638-47-7 80648-16-4 83329-17-3
RL: PROC (Process)
(opiate receptor binding of, structure in relation to)

L73 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1982:63137 HCAPLUS
DN 96:63137
ED Entered STN: 12 May 1984
TI Structural requirements for specific recognition of .mu. or .delta. opiate receptors
AU Fournie-Zaluski, Marie Claude; Gacel, Gilles; Maigret, Bernard; Premilat, Samuel; Roques, Bernard P.
CS Dep. Chim. Org., CNRS, Paris, 75006, Fr.
SO Molecular Pharmacology (1981), 20(3), 484-91
CODEN: MOPMA3; ISSN: 0026-895X
DT Journal
LA English
CC 2-2 (Mammalian Hormones)

AB A comparison of the inhibitory potency of new analogs of enkephalins on the evoked contractions of guinea pig ileum (μ . receptors) and mouse vas deferens (δ . receptors) allows the definition of the structural components required for specific recognition of μ . or δ . receptors. A high specificity for μ . binding sites is obtained by shortening the enkephalin sequence and removing the terminal carboxyl group, by replacing the aromatic Phe4 residue with a lipophilic alkyl chain, and by introducing as a 2nd residue a hydrophobic amino acid of the D-configuration whose side-chain probably interacts with a specific μ .-receptor subsite. Compared with methionine-enkephalin [58569-55-4] such modifications lead to a 99% loss of potency on mouse vas deferens but a 2-fold enhanced activity on guinea pig ileum. These short peptides display a high folding tendency. The low-energy conformer of the highest μ .-specific peptide exhibits a T-shaped structure similar to that of morphine. All of the proposed μ .-specific requirements account for the reported variations in the biol. activity of various modified enkephalins. The μ .-agonist potency of endogenous enkephalins was related to a fitting of the side-chain of their 5th amino acid in the μ . hydrophobic subsite. The requirements for δ . receptor specificity are even more strict and involve an aromatic moiety in the 4th position, a conformational key role of the amino acid(s) following the Phe4, improving the fitting of the Phe4 side-chain in a specific δ .-receptor subsite, and a lengthening of the enkephalin sequence and the introduction of a hydrophilic side-chain in position 2 which decrease the μ . specificity. These modifications lead to peptides almost 3 orders of magnitude more active on mouse vas deferens than on guinea pig ileum. μ . Receptors bind preferentially highly hydrophobic compds. with compact structures, whereas δ . receptors exhibit a stronger affinity for larger peptides with hydrophilic components. Thus 3H-labeled Tyr-D-Ser-Gly-Phe-Leu-Thr, the most selective δ . agonist, interacts exclusively with δ .-binding sites at concns. up to 20 nM. In contrast, Tyr-D-Ala-Gly-NH-CH(CH3)-CH2-CH(CH3)2 exhibits a specificity almost 50 times greater for μ . receptors than for δ . receptors.

ST enkephalin analog opiate receptor; conformation peptide opiate receptor

IT Enkephalins
RL: BIOL (Biological study)
(analogs, opiate activity of, structure in relation to)

IT Receptors
RL: BIOL (Biological study)
(for opiates, enkephalin analogs binding by, structural requirements for)

IT Conformation and Conformers
(of enkephalin analogs, opiate receptors binding in relation to)

IT Receptors
RL: BIOL (Biological study)
(σ -, enkephalins binding by, structural requirements for)

IT Molecular structure-biological activity relationship
(opiate receptor-binding, of enkephalin analogs)

IT Receptors
RL: BIOL (Biological study)
(μ -, enkephalins binding by, structural requirements for)

IT 58569-55-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(opiate activity of, enkephalin analogs in relation to)

IT 57-27-2, biological studies 58569-55-4 58822-25-6
60117-18-2 61370-87-4 63631-40-3 64963-01-5 66609-07-2
66649-46-5 67706-17-6 68905-83-9 72732-16-2 72732-17-3
72732-18-4 75644-90-5 80638-46-6 80638-47-7 80648-16-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(opiate activity of, structure in relation to)

L73 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1976:22038 HCAPLUS

DN 84:22038

ED Entered STN: 12 May 1984

TI Characteristics of ambiphile salves and cream foundations

AU Nuernberg, Eberhard

CS Inst. Pharm. Technol., Fa. E. Merck, Darmstadt, Fed. Rep. Ger.

SO Pharmazeutische Zeitung (1975), 120(39), 1509-19

CODEN: PHZIAP; ISSN: 0031-7136

DT Journal

LA German

CC 63-5 (Pharmaceuticals)

AB The elec. conductivity, isothermal moisture evaporation, and agar diffusion behavior of hydrophilic, lipophilic, and ambiphilic cream bases, and their in vitro release of salicylic acid [69-72-7] and gentamycin sulfate [1405-41-0] were studied. In spite of their lower hydrophilicity, the ambiphilic cream bases showed release properties which were as favorable or even more favorable than those of an oil-in-water system.

ST cream ambiphile release property

IT Cosmetics
Pharmaceuticals
(ambiphilic cream foundations for, properties of)

IT Ointments
(ambiphilic, properties of)

IT 69-72-7, properties 1405-41-0
RL: PRP (Properties)
(release of, by ambiphilic creams)

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on STN

AN 1998275834 EMBASE

TI A system for the brain-enhanced delivery of estradiol: An assessment of its potential for the treatment of Alzheimer's disease and stroke.

AU Simpkins J.W.; Rabbani O.; Shi J.; Panickar K.S.; Green P.S.; Day A.L.

CS Dr. J.W. Simpkins, College of Pharmacy, University of Florida, Gainesville, FL 32610, United States

SO Pharmazie, (1998) 53/8 (505-511).

Refs: 88

ISSN: 0031-7144 CODEN: PHARAT

CY Germany

DT Journal; General Review

FS 008 Neurology and Neurosurgery

027 Biophysics, Bioengineering and Medical Instrumentation

030 Pharmacology

037 Drug Literature Index

LA English

CT Medical Descriptors:

*alzheimer disease

*stroke

*brain

*drug delivery system

cholinergic nerve cell

lipophilicity

blood brain barrier

hydrophilicity

lipid solubility

hydrolysis

oxidation reduction reaction

enzyme activity

neuroprotection

membrane depolarization

calcium homeostasis

human

nonhuman

review

Drug Descriptors:

*estradiol: AN, drug analysis

*estradiol: PK, pharmacokinetics

*estradiol: PD, pharmacology

*dihydropyridine

*pyridinium derivative

*3 hydroxy 17beta [(1 methyl 1,4 dihydropyridine 3 yl)carbonyl]oxylestra

1,3,5 (10) triene: AN, drug analysis

*1 methyl 3 [[(3 hydroxyestra 1,3,5 (10) triene 17beta
yl)oxy]carbonyl]pyridinium iodide: AN, drug analysis
thromboxane: EC, endogenous compound
lipid: EC, endogenous compound
glucose: EC, endogenous compound
oxygen: EC, endogenous compound
excitatory amino acid: TO, drug toxicity
choline acetyltransferase: EC, endogenous compound
choline: EC, endogenous compound
calcium: EC, endogenous compound
cyclic amp responsive element binding protein: EC, endogenous compound
messenger rna: EC, endogenous compound
neurotrophin receptor: EC, endogenous compound
neurotrophin: EC, endogenous compound
mitogen activated protein kinase: EC, endogenous compound
nerve growth factor: EC, endogenous compound
amyloid beta protein: TO, drug toxicity
glutamic acid: TO, drug toxicity
buthionine sulfoximine: TO, drug toxicity
hydrogen peroxide: TO, drug toxicity
glucose transporter: EC, endogenous compound
diethylstilbestrol
neurotransmitter: EC, endogenous compound
unclassified drug

RN (estradiol) 50-28-2; (dihydropyridine) 27790-75-6; (thromboxane)
66719-58-2; (lipid) 66455-18-3; (glucose) 50-99-7, 84778-64-3; (oxygen)
7782-44-7; (choline acetyltransferase) 9012-78-6; (choline) 123-41-1,
13232-47-8, 1927-06-6, 4858-96-2, 62-49-7, 67-48-1; (calcium) 7440-70-2;
(cyclic amp responsive element binding protein) 130428-87-4, 130939-96-7;
(mitogen activated protein kinase) 142243-02-5; (nerve growth factor)
9061-61-4; (amyloid beta protein) 109770-29-8; (glutamic acid) 11070-68-1,
138-15-8, 56-86-0, 6899-05-4; (buthionine sulfoximine) 5072-26-4;
(hydrogen peroxide) 7722-84-1; (diethylstilbestrol) 30498-85-2, 56-53-1

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L93 ANSWER 1 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
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AN 1998344063 EMBASE

TI Mechanism of action of chromogranin A on catecholamine release: Molecular
modeling of the catestatin region reveals a .beta.-strand/loop/.beta.-
strand structure secured by hydrophobic interactions and predictive of
activity.

AU Tsigelny I.; Mahata S.K.; Taupenot L.; Preece N.E.; Mahata M.; Khan I.;
Parmer R.J.; O'Connor D.T.

CS D.T. O'Connor, Department of Medicine, Center for Molecular Genetics,
University of California, San Diego, CA, United States. doconnor@ucsd.edu

SO Regulatory Peptides, (1998) 77/1-3 (43-53).

Refs: 37

ISSN: 0167-0115 CODEN: REPPDY

PUI S 0167-0115(98)00040-8

CY Netherlands

DT Journal; Article

FS 029 Clinical Biochemistry

LA English

SL English

AB A novel fragment of chromogranin A, known as 'catestatin' (bovine
chromogranin A344-364), inhibits catecholamine release from chromaffin
cells and noradrenergic neurons by acting as a non-competitive nicotinic
cholinergic antagonist, and may therefore constitute an endogenous
autocrine feedback regulator of sympathoadrenal activity. To characterize
how this activity depends on the peptide's structure, we searched for
common 3-dimensional motifs for this primary structure or its homologs.
Catestatin's primary structure bore significant (29-35.5% identity,
general alignment score 44-57) sequence homology to fragment sequences
within three homologs of known 3-dimensional structures, based on solved
X-ray crystals: 8FAB, 1PKM, and 2IG2. Each of these sequences exists in
nature as a .beta.-strand/loop/.beta.-strand structure, stabilized by
hydrophobic interactions between the .beta.-strands. The catestatin
structure was stable during molecular dynamics simulations. The catestatin
loop contains three Arg residues, whose electropositive side chains form
the terminus of the structure, and give rise to substantial uncompensated
charge asymmetry in the molecule. A hydrophobic moment plot revealed that
catestatin is the only segment of chromogranin A predicted to contain
amphiphilic .beta.-strand. Circular dichroism in the far

ultraviolet showed substantial (63%) .beta.-sheet structure, especially in a hydrophobic environment. Alanine-substitution mutants of catestatin established a crucial role for the three central arginine residues in the loop (Arg351, Arg353, and Arg358), though not for two arginine residues in the strand region toward the amino-terminus. [125I]Catestatin bound to Torpedo membranes at a site other than the nicotinic agonist binding site. When the catestatin structure was 'docked' with the extracellular domain of the Torpedo nicotinic cholinergic receptor, it interacted principally with the .beta. and .delta. subunits, in a relatively hydrophobic region of the cation pore extracellular orifice, and the complex of ligand and receptor largely occluded the cation pore, providing a structural basis for the non-competitive nicotinic cholinergic antagonist properties of the peptide. We conclude that a homology model of catestatin correctly predicts actual features of the peptide, both physical and biological. The model suggests particular spatial and charge features of the peptide which may serve as starting points in the development of non-peptide mimetics of this endogenous nicotinic cholinergic antagonist. Copyright (C) 1998 Elsevier Science B.V.

CT Medical Descriptors:

*catecholamine release

*molecular model

protein structure

chromaffin granule

chromaffin cell

molecular dynamics

circular dichroism

membrane binding

article

priority journal

Drug Descriptors:

*chromogranin a: EC, endogenous compound

catestatin: EC, endogenous compound

nicotinic receptor: EC, endogenous compound

catecholamine: EC, endogenous compound

unclassified drug

L93 ANSWER 2 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN

AN 97297410 EMBASE

DN 1997297410

TI Molecular simulation of dynorphin A-(1-10) binding to extracellular loop 2 of the .kappa.-opioid receptor. A model for receptor activation.

AU Paterlini G.; Portoghesi P.S.; Ferguson D.M.

CS G. Paterlini, DMCMSI, University of Minnesota, Minneapolis, MN 55455, United States

SO Journal of Medicinal Chemistry, (1997) 40/20 (3254-3262).

Refs: 58

ISSN: 0022-2623 CODEN: JMCMAR

CY United States

DT Journal; Article

FS 030 Pharmacology

037 Drug Literature Index

LA English

SL English

AB The structure of the second extracellular loop region (EL2) of the .kappa.-opioid receptor has been explored in an effort to understand the structural basis for dynorphin A binding and selectivity. Application of secondary structure prediction methods and homology modeling resulted in a turn-helix motif for the N-terminal region of .kappa.-EL2. A similar motif was not predicted for EL2 of either the .delta. or .mu. opioid receptors. The EL2 helix was further shown to be amphiphilic and complementary to the helical component of dynorphin A. Using a model of the .kappa.-receptor (Metzger et al. Neurochem. Res. 1996, 21, 1287-1294), including the newly predicted EL2 turn-helix domain, a binding mode is proposed based on helix-helix interactions between hydrophobic residues of EL2 and the helical component of dynorphin A-(1-10). Molecular simulations of the receptor-ligand complex yielded structures in which the tyramine moiety or opioid 'message' of dynorphin is bound within a conserved aromatic pocket in the transmembrane domain while the helical portion contacted residues in EL2 and in the extracellular end of transmembrane helices 6 and 7. The model is in general agreement with site-directed mutagenesis data and chimera studies that have identified binding domains in both the EL2 and transmembrane regions to dynorphin A. The results confirm the importance of the opioid 'message' displayed by many opioid ligands but also suggest a potential mechanism of receptor activation that may be mediated by EL2 through interactions with the 'address' component

of dynorphin A.

CT Medical Descriptors:
 *drug receptor binding
 article
 drug structure
 molecular model
 protein secondary structure
 site directed mutagenesis
 Drug Descriptors:
 *dynorphin a derivative: AN, drug analysis
 *dynorphin a derivative: PD, pharmacology
 *dynorphin[1-10]: AN, drug analysis
 *dynorphin[1-10]: PD, pharmacology
 *kappa opiate receptor
 unclassified drug

RN (dynorphin[1-10]) 79994-24-4

L93 ANSWER 3 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN

AN 96172594 EMBASE
 DN 1996172594

TI 2-Alkyl-substituted histamines and hydroxyethylimidazoles with
 G-protein-stimulatory activity.

AU Detert H.; Leschke C.; Togel W.; Seifert R.; Schunack W.
 CS Institut fur Organische Chemie, Johannes Gutenberg-Universitat,
 Johann-Joachim-Becher-Weg 18-20, D-55099 Mainz, Germany
 SO European Journal of Medicinal Chemistry, (1996) 31/5 (397-405).
 ISSN: 0223-5234 CODEN: EJMCA5

CY France
 DT Journal; Article
 FS 026 Immunology, Serology and Transplantation
 029 Clinical Biochemistry
 037 Drug Literature Index

LA English
 SL English

AB Cationic-amphiphilic 2-substituted histamines activate pertussis
 toxin-sensitive guanine nucleotide-binding proteins (G-proteins) by a
 receptor-independent mechanism. From our recent studies it became apparent
 that lipophilicity is an important determinant for this G-protein
 activation, but the influence of basicity remained unknown. We prepared
 seven novel 2-alkyl-substituted histamines and five novel
 2-alkyl-substituted hydroxyethylimidazoles and studied their effects on
 high-affinity guanosine triphosphate (GTP) hydrolysis in membranes of the
 human leukemia cell line, HL-60. 2-Octylhistamine was found to be the most
 effective GTPase activator among 2-substituted histamines presently
 available (150% stimulation above basal), and 2-tetradecylhistamine is the
 most potent substance in this regard (pEC50 = 5.9). Branching of the alkyl
 chain and the introduction of an ether group adversely affected GTPase
 activation. Compared to a phenyl ring, a bulky adamantyl sphere enhanced
 G-protein-stimulatory activity. In the case of 2-(3-bromophenyl)histamine,
 2-adamantylhistamine and 2-(3-phenylpropyl)histamine, replacement of the
 aminoethyl group by a hydroxyethyl group at the imidazole greatly reduced
 GTPase-activating properties, pointing to the importance of the basic
 domain in the activation process. Unexpectedly, however, in the case of a
 very lipophilic substituent (heptadecyl chain) the exchange of the
 aminoethyl group by a hydroxyethyl group had no substantial inhibitory
 effect, indicating that the presence of a primary amine is not a conditio
 sine qua non for a substance being a receptor-independent G-protein
 activator. Concerning histamine H1-receptors the newly prepared compounds
 proved to be weak antagonists.

CT Medical Descriptors:
 *cell membrane
 *enzyme activation
 animal tissue
 article
 controlled study
 drug receptor binding
 drug synthesis
 guinea pig
 human
 human cell
 ileum
 leukemia cell line
 lipophilicity
 nonhuman
 structure activity relation

Drug Descriptors:

*guanine nucleotide binding protein: EC, endogenous compound
 *guanosine triphosphatase: EC, endogenous compound
 *histamine derivative: AN, drug analysis
 *histamine derivative: CM, drug comparison
 *histamine derivative: DV, drug development

*histamine h2 receptor: EC, endogenous compound
 2 octylhistamine: AN, drug analysis
 2 octylhistamine: CM, drug comparison
 2 octylhistamine: DV, drug development
 3 (2 hydroxyethyl)imidazole derivative: DV, drug development
 3 (2 hydroxyethyl)imidazole derivative: AN, drug analysis
 3 (2 hydroxyethyl)imidazole derivative: CM, drug comparison
 pertussis toxin

unclassified drug

RN (guanosine triphosphatase) 9059-32-9; (pertussis toxin) 70323-44-3

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on STN

AN 96152859 EMBASE

DN 1996152859

TI A galanin-mastoparan chimeric peptide activates the Na⁺, K⁺-ATPase and reverses its inhibition by ouabain.

AU Langel U.; Pooga M.; Kairane C.; Zilmer M.; Bartfai T.

CS Dept. Neurochemistry/Neurotoxicology, Arrheniuslaboratories, Stockholm University, S-106 91 Stockholm, Sweden

SO Regulatory Peptides, (1996) 62/1 (47-52).

ISSN: 0167-0115 CODEN: REPPDY

CY Netherlands

DT Journal; Article

FS 002 Physiology

008 Neurology and Neurosurgery

029 Clinical Biochemistry

037 Drug Literature Index

LA English

SL English

AB The effect of the neuropeptide galanin, the wasp venom toxin amphiphilic peptide toxin mastoparan and the chimeric peptide, galparan, consisting of N-terminal 13 amino acids of neuropeptide galanin linked at C-terminus to mastoparan amide (and its inactive analog Mas17) on the activity of Na⁺,K⁺-ATPase has been studied. Mastoparan inhibits the activity of the Na⁺,K⁺-ATPase with IC₅₀ = 7.5 .mu.M and also reduces the cooperativity for Na⁺ and K⁺, respectively, while galanin has no effect on the Na⁺,K⁺-ATPase activity. The chimeric peptide, galanin(1-13)-mastoparan amide (galparan), exhibits biphasic interaction with Na⁺,K⁺-ATPase, it activates the enzyme at maximal stimulating concentration of 4 .mu.M followed by inhibition of the enzyme with IC₅₀, of 100 .mu.M. At maximum stimulating concentration (4 .mu.M), galparan partly reduces the cooperativity only for Na⁺ and it also counteracts the inhibitory effect of ouabain on Na⁺,K⁺-ATPase. Galparan's stimulatory effect was influenced by ATP. The chimeric peptide [19Lys,26Leu]-galparan, containing the inactive analog of mastoparan (Mas17), has no effects on rat brain Na⁺,K⁺-ATPase activity. Both chimeric peptides galparan and [19Lys,26Leu]-galparan are high-affinity galanin receptor ligands with IC₅₀ of 6.4 nM and 0.71 nM, respectively, while galanin (1-13) and mastoparan alone have significantly lower affinity for the galanin receptor, IC₅₀ Of 125 nM and 1 .mu.M, respectively. The ability of chimeric peptides to bind to galanin receptors does not correlate with their effects on the Na⁺,K⁺-ATPase.

CT Medical Descriptors:

*enzyme activity

*frontal cortex

animal tissue

article

binding site

drug receptor binding

membrane binding

nonhuman

priority journal

rat

Drug Descriptors:

*galanin: PD, pharmacology

*galanin derivative: PD, pharmacology

*mastoparan: PD, pharmacology

*ouabain

adenosine triphosphatase (potassium sodium): EC, endogenous compound

adenosine triphosphate
 chimeric protein
 galanin receptor: EC, endogenous compound
 galparan: PD, pharmacology
 neuropeptide
 wasp venom
 unclassified drug

RN (galanin) 88813-36-9; (mastoparan) 72093-21-1; (ouabain) 11018-89-6,
 630-60-4; (adenosine triphosphate) 15237-44-2, 56-65-5, 987-65-5

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 on STN

AN 96074849 EMBASE

DN 1996074849

TI G-Protein-coupled receptors in HL-60 human leukemia cells.

AU Klinker J.F.; Wenzel-Seifert K.; Seifert R.

CS Howard Hughes Medical Institute, Stanford University, Medical
 Center, Stanford, CA 94305, United States

SO General Pharmacology, (1996) 27/1 (33-54).

ISSN: 0306-3623 CODEN: GEPHDP

CY United States

DT Journal; General Review

FS 016 Cancer

025 Hematology

029 Clinical Biochemistry

030 Pharmacology

037 Drug Literature Index

LA English

SL English

AB 1. HL-60 human leukemia cells are a widely employed model system for the
 analysis of signal transduction processes mediated via regulatory
 heterotrimeric guanine nucleotide-binding proteins (G-proteins). HL-60
 promyelocytes are pluripotent and can be differentiated into neutrophilic
 or monocytic cells. 2. HL-60 cells express formyl peptide-, complement
 C5a-, leukotriene B4 (LTB4)- and platelet-activating factor receptors,
 receptors for purine and pyrimidine nucleotides, histamine H1- and
 H2-receptors .beta.2-adrenoceptors and prostaglandin receptors. 3. The
 major G-proteins in HL-60 cells are pertussis toxin (PTX) sensitive
 G(i)-proteins (G(i2) > G(i3)). G(s)-proteins and G-proteins of the
 G(q)-family (e.g., G16) are expressed, too. 4. G-protein-regulated
 effector systems in HL-60 cells are adenylyl cyclase and phospholipase
 C-.beta.2 (PLC-.beta.2) and, possibly, phospholipase D (PLD), nonselective
 cation (NSC) channels and NADPH oxidase. 5. The expression of signal
 transduction pathways in HL-60 cells strongly depends on the
 differentiation state of cells. 6. Formyl peptides, via G(i) proteins,
 mediate activation of PLC, PLD, NSC channels, NADPH oxidase and
 azurophilic granule release and are referred to as full secretagogues. In
 dibutyryl cAMP (Bt2cAMP)-differentiated HL-60 cells, C5a and LTB4 are
 partial and incomplete secretagogues, respectively. There are substantial
 differences in the G(i)-protein activations induced by formyl peptides,
 C5a and LTB4. 7. In HL-60 promyelocytes, purine and pyrimidine nucleotides
 mediate activation of PLC and NSC channels largely via PTX-insensitive
 G-proteins and induce functional differentiation. In Bt2cAMP-
 differentiated HL-60 cells, they additionally activate PLD, NADPH oxidase
 and granule release via PTX-sensitive and -insensitive pathways. ATP and
 UTP are partial secretagogues. Multiple types of receptors (i.e., P(2Y)-
 and P(2U)-receptors and pyrimidinocyeptors) may mediate the effects of
 nucleotides in HL-60 cells. 8. Bt2cAMP and 1.alpha.,25-
 dihydroxycholecalciferol-differentiated HL-60 cells express H1- receptors
 coupled to G(i)-proteins and PTX-insensitive G-proteins. In the former
 cells, histamine mediates activation of PLC and NSC channels, and in the
 latter, activation of NSC channels. Histamine is an incomplete
 secretagogue in these cells. 9. HL-60 promyelocytes express H2-receptors
 coupled to adenylyl cyclase, PLC, and NSC channels. There are substantial
 differences in the agonist/antagonist profiles of H2-receptors receptor
 mediated cAMP formation and rises in cytosolic Ca2+ concentration,
 indicative of the involvement of different H2-receptors receptor subtypes.
 H2-receptors mediate functional differentiation of HL-60 cells. 10.
 Certain cationic-amphiphilic histamine receptor ligands (i.e., 2
 substituted histamines, lipophilic guanidines, and a histamine
 trifluoromethyl toluidide derivative) show stimulatory effects in HL-60
 cells that are attributable to receptor independent activation of
 G(i)-proteins.

CT Medical Descriptors:

*leukemia cell

*signal transduction

cation channel
 cell differentiation
 cell strain hl 60
 human
 human cell
 model
 monocyte
 neutrophil
 priority journal
 promyelocyte
 review

Drug Descriptors:

*adenylate cyclase: EC, endogenous compound
 *guanine nucleotide binding protein: EC, endogenous compound
 *phospholipase c: EC, endogenous compound
 *receptor: EC, endogenous compound
 adenosine triphosphate: PD, pharmacology
 beta 2 adrenergic receptor: EC, endogenous compound
 bucladesine: PD, pharmacology
 calcitriol: PD, pharmacology
 complement component c5a: PD, pharmacology
 complement component c5a receptor: EC, endogenous compound
 formylpeptide: PD, pharmacology
 formylpeptide receptor: EC, endogenous compound
 histamine: PD, pharmacology
 histamine derivative: PD, pharmacology
 histamine h1 receptor: EC, endogenous compound
 histamine h2 receptor: EC, endogenous compound
 inhibitory guanine nucleotide binding protein: EC, endogenous compound
 leukotriene b4: PD, pharmacology
 leukotriene b4 receptor: EC, endogenous compound
 pertussis toxin: TO, drug toxicity
 phospholipase d: EC, endogenous compound
 prostaglandin receptor: EC, endogenous compound
 purine nucleotide: PD, pharmacology
 purine receptor: EC, endogenous compound
 pyrimidine nucleotide: PD, pharmacology
 reduced nicotinamide adenine dinucleotide phosphate oxidase: EC, endogenous compound
 stimulatory guanine nucleotide binding protein: EC, endogenous compound
 thrombocyte activating factor receptor: EC, endogenous compound
 unindexed drug
 uridine triphosphate: PD, pharmacology
 unclassified drug

RN (adenylate cyclase) 9012-42-4; (phospholipase c) 9001-86-9; (adenosine triphosphate) 15237-44-2, 56-65-5, 987-65-5; (bucladesine) 16980-89-5, 362-74-3; (calcitriol) 32222-06-3, 32511-63-0, 66772-14-3; (histamine) 51-45-6, 56-92-8, 93443-21-1; (leukotriene b4) 71160-24-2; (pertussis toxin) 70323-44-3; (phospholipase d) 9001-87-0; (reduced nicotinamide adenine dinucleotide phosphate oxidase) 9032-22-8; (uridine triphosphate) 63-39-8

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 on STN

AN 95364319 EMBASE

DN 1995364319

TI Targeted transfection of human hepatoma cells with a combination of lipospermine and neo-galactolipids.

AU Kichler A.; Remy J.-S.; Behr J.-P.; Schuber F.

CS Laboratoire de Chimie Bioorganique, Faculte de Pharmacie, CNRS URA 1386, 74 Route du Rhin, 67401 Strasbourg-Illkirch Cedex, France

SO Journal of Liposome Research, (1995) 5/4 (735-745).

ISSN: 0898-2104 CODEN: JLREE7

CY United States

DT Journal; Article

FS 029 Clinical Biochemistry

030 Pharmacology

037 Drug Literature Index

LA English

SL English

AB Optimal in vitro gene delivery with (poly)cationic amphiphiles requires an excess of cationic charges with respect to DNA phosphates. We have developed targeted transfection systems based on electrically neutral lipospermine/DNA particles, to which synthetic tri-antennary galactose ligands were conjugated to provide an interaction with cells, such as HepG2 cells, that express Gal/GalNAc receptors at their surface.

Transfection, which was cell specific, increases .simeq. 1000-fold with 25% neogalactolipid, i.e. approaching the value observed with optimized positively charged transfection complexes. Unexpectedly, neutral particles containing thiol-reactive phospholipids, were also efficient gene delivery systems, although non cell specific.

CT Medical Descriptors:

*gene targeting
 *hepatoma cell: DT, drug therapy
 *genetic transfection
 article
 binding affinity
 binding site
 gene induction
 gene therapy
 opsonization
 plasmid
 priority journal
 Drug Descriptors:

cell surface receptor

*amphophile: PR, pharmaceuticals
 *liposome: CB, drug combination
 *liposome: DV, drug development
 *spermine: CB, drug combination
 *spermine: DV, drug development
 *spermine: DT, drug therapy
 *spermine: PR, pharmaceuticals
 lipospermine
 transfectam

unclassified drug

RN (spermine) 306-67-2, 71-44-3
 CN (1) Transfectam
 CO (1) Promega

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 on STN

AN 95321821 EMBASE

DN 1995321821

TI The amphiphilic peptide adenoregulin enhances agonist binding to A1- adenosine receptors and [35S]GTP.gamma.S to brain membranes.

AU Moni R.W.; Romero F.S.; Daly J.W.

CS National Institutes of Health, Bldg. 8, Bethesda, MD 20892, United States

SO Cellular and Molecular Neurobiology, (1995) 15/4 (465-493).

ISSN: 0272-4340 CODEN: CMNEDI

CY United States

DT Journal; Article

FS 008 Neurology and Neurosurgery

029 Clinical Biochemistry

LA English

SL English

AB 1. Adenoregulin is an amphiphilic peptide isolated from skin mucus of the tree frog, *Phyllomedusa bicolor*. Synthetic adenoregulin enhanced the binding of agonists to several G-protein-coupled receptors in rat brain membranes. 2. The maximal enhancement of agonist binding, and in parentheses, the concentration of adenoregulin affording maximal enhancement were as follows: 60% (20 .mu.M) for A1-adenosine receptors, 30% (100 .mu.M) for A(2a)-adenosine receptors, 20% (2 .mu.M) for .alpha.2-adrenergic receptors, and 30% (10 .mu.M) for 5HT(1A) receptors. High affinity agonist binding for A1-, .alpha.2-, and 5HT(1A)-receptors was virtually abolished by GTP.gamma.S in the presence of adenoregulin, but was only partially abolished in its absence. Magnesium ions increased the binding of agonists to receptors and reduced the enhancement elicited by adenoregulin. 3. The effect of adenoregulin on binding of N6-cyclohexyladenosine ([3H]CHA) to A1-receptors was relatively slow and was irreversible. Adenoregulin increased the B(max) value for [3H]CHA binding sites, and the proportion of high affinity states, and slowed the rate of [3H]CHA dissociation. Binding of the A1-selective antagonist, [3H]DPCPX, was maximally enhanced by only 13% at 2 .mu.M adenoregulin. Basal and A1-adenosine receptor-stimulated binding of [35S]GTP.gamma.S were maximally enhanced 45% and 23%, respectively, by 50 .mu.M adenoregulin. In CHAPS-solubilized membranes from rat cortex, the binding of both [3H]CHA and [3H]DPCPX were enhanced by adenoregulin. Binding of [3H]CHA to membranes from DDT1 MF-2 cells was maximally enhanced 17% at 20 .mu.M adenoregulin. In intact DDT1 MF-2 cells, 20 .mu.M adenoregulin did not potentiate the inhibition of cyclic AMP accumulation mediated via the adenosine A1 receptor. 4. It is proposed that adenoregulin enhances agonist binding through a mechanism involving enhancement of guanyl nucleotide exchange at

G- proteins, resulting in a conversion of receptors into a high affinity state complexed with guanyl nucleotide-free G-protein.

CT Medical Descriptors:
 *brain membrane
 *receptor binding
 animal tissue
 article
 binding kinetics
 brain cortex
 cerebellum
 controlled study
 corpus striatum
 frog
 hippocampus
 nonhuman
 priority journal
 rat
 receptor affinity
 Drug Descriptors:
 *adenosine a1 receptor
 alpha 2 adrenergic receptor
 serotonin 1a receptor
 *amphophile
 *guanine nucleotide binding protein: EC, endogenous compound
 *guanosine 5' o (3 thiotriphosphate)
 *peptide
 8 cyclopentyl 1,3 dipropylxanthine
 adenoregulin
 cyclic amp: EC, endogenous compound
 cyclohexyladenosine
 magnesium ion
 sodium chloride
 unclassified drug

RN (guanosine 5' o (3 thiotriphosphate)) 37589-80-3; (8 cyclopentyl 1,3 dipropylxanthine) 102146-07-6; (cyclic amp) 60-92-4; (cyclohexyladenosine) 36396-99-3; (magnesium ion) 22537-22-0; (sodium chloride) 7647-14-5

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AN 95176244 EMBASE
 DN 1995176244

TI The cholesterol derivative of a triantennary galactoside with high affinity for the hepatic asialoglycoprotein receptor: A potent cholesterol lowering agent.

AU Biessen E.A.L.; Broxterman H.; Van Boom J.H.; Van Berkel T.J.C.
 CS Division of Biopharmaceutics, Leiden-Amsterdam Drug Research Ctr., P.O. Box 9503, 2300 RA Leiden, Netherlands
 SO Journal of Medicinal Chemistry, (1995) 38/11 (1846-1852).
 ISSN: 0022-2623 CODEN: JMCMAR

CY United States
 DT Journal; Article
 FS 018 Cardiovascular Diseases and Cardiovascular Surgery
 030 Pharmacology
 037 Drug Literature Index

LA English
 SL English

AB Cholesterol-derivatized galactosides have been devised in order to induce liver uptake of lipoproteins via the galactose-recognizing asialoglycoprotein receptor in the liver. In this study we describe the derivatization of a newly developed triantennary cluster galactoside having high affinity for the asialoglycoprotein receptor, N-[[[tris-O-(3,6,9-trioxoundecanyl-.beta.-D- galactopyranosyl)methoxymethyl]methyl]-N(n)-[1-(6-methyladipyl)]glycinamide (TG(20.ANG.)) with cholesterol. Hereto, TG(20.ANG.) was coupled to glycine-(5-cholesten-3.beta.-yl ester) in the presence of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate, affording N-[[[tris-O-(3,6,9-trioxoundecanyl-.beta.-D-galactopyranosyl)methoxymethyl]methyl]-N(.alpha.)-[1-(6-(5-cholesten-3.beta.-yloxy)glycyl)adipyl]glycinamide (TG(20.ANG.)C) in 46% yield. This compound is an amphiphilic, water-soluble compound. In aqueous solution it readily formed small micelles (4.9 +/- 1.2 nm) consisting of approximately 20 molecules. Upon incubation with human serum, TG(20.ANG.)C spontaneously incorporated into the most prominent serum lipoproteins, i.e., low-density lipoprotein (LDL) and high-density lipoprotein (HDL), thereby inducing an increase in buoyant density of these lipoproteins. The integrity of HDL and LDL, as judged from particle size analysis of both lipoproteins, was not altered

by incubation with up to 0.33% of TG(20.ANG.)C (w/v). Following intravenous bolus injection into rats, TG(20.ANG.)C induced a dose-dependent decrease in the serum cholesterol content of maximally 44%, at a dose of 1.9 mg kg⁻¹. This makes TG(20.ANG.)C at least 30-fold more effective than the previously developed .cntdot. N-[[[tris-O-(.beta.-D-galactopyranosyl)methyl]methyl]- N(.alpha.) [4-(5-cholesten-3.beta.-yloxy)succinyl]glycinamide (TG(4.ANG.)C), provided with a cluster galactoside that displayed a 2000-fold lower affinity for the asialoglycoprotein receptor than TG(20.ANG.). In conclusion, the hypocholesterolemic activity of a cholesterylated galactoside can be strongly enhanced by using a cluster galactoside with higher affinity for the asialoglycoprotein receptor.

CT Medical Descriptors:

*drug receptor binding
 *hypercholesterolemia
 animal experiment
 article
 cholesterol liver level
 cholesterol transport
 dose response
 drug potency
 drug synthesis
 human
 male
 nonhuman
 rat
 receptor affinity

Drug Descriptors:

*asialoglycoprotein receptor
 *hypocholesterolemic agent: DV, drug development
 *hypocholesterolemic agent: DO, drug dose
 *hypocholesterolemic agent: PD, pharmacology
 *hypocholesterolemic agent: CM, drug comparison
 (benzotriazol 1 yloxy)tris(dimethylamino)phosphonium hexafluorophosphate:
 DV, drug development
 glycine 5 cholesten 3beta yl ester: DV, drug development
 n [[[[tris o (beta d galactopyranosyl) 3,6,9 trioxaundecanoxylmethoxy]methy
 l] n alpha [1 (6 methyladipyl)]glycinamide: DV, drug development
 n [[[[tris o (beta d galactopyranosyl) 3,6,9 trioxaundecanoxylmethoxy]methy
 l] n alpha [1 (6 methyladipyl)]glycinamide: DO, drug dose
 n [[[[tris o (beta d galactopyranosyl) 3,6,9 trioxaundecanoxylmethoxy]methy
 l] n alpha [1 (6 methyladipyl)]glycinamide: PD, pharmacology
 n [tris o (3,6,9 trioxaundecanyl beta d galactopyranosyl)methoxymethyl]met
 hyl n alpha [1 [6 (5 cholesten 3beta yloxy)glycyl]adipyl]glycinamide: DV,
 drug development
 n [tris o (3,6,9 trioxaundecanyl beta d galactopyranosyl)methoxymethyl]met
 hyl n alpha [1 [6 (5 cholesten 3beta yloxy)glycyl]adipyl]glycinamide: PD,
 pharmacology
 n [tris o (3,6,9 trioxaundecanyl beta d galactopyranosyl)methoxymethyl]met
 hyl n alpha [1 [6 (5 cholesten 3beta yloxy)glycyl]adipyl]glycinamide: DO,
 drug dose
 n [tris o (3,6,9 trioxaundecanyl beta d galactopyranosyl)methoxymethyl]met
 hyl n alpha [1 [6 (5 cholesten 3beta yloxy)glycyl]adipyl]glycinamide: CM,
 drug comparison
 n [tris o (beta d glucopyranosyl)methyl]methyl n alpha [4 o (5 cholesten
 3beta yl)succinyl]glycinamide: CM, drug comparison
 n [tris o (beta d glucopyranosyl)methyl]methyl n alpha [4 o (5 cholesten
 3beta yl)succinyl]glycinamide: DV, drug development
 n [tris o (beta d glucopyranosyl)methyl]methyl n alpha [4 o (5 cholesten
 3beta yl)succinyl]glycinamide: DO, drug dose
 n [tris o (beta d glucopyranosyl)methyl]methyl n alpha [4 o (5 cholesten
 3beta yl)succinyl]glycinamide: PD, pharmacology

unclassified drug

CO Bissendorf (Germany)

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AN 95091592 EMBASE

DN 1995091592

TI Cationic-amphiphilic arpromidine-derived guanidines and a
histamine trifluoromethyl-toluidine derivative may activate pertussis
toxin-sensitive G-proteins by a receptor-independent mechanism.AU Hagelucken A.; Burde R.; Nurnberg B.; Harhammer R.; Buschauer A.; Seifert
R.CS Institut fur Pharmazie, Universitat Regensburg, D-93040 Regensburg, Germany
SO Naunyn-Schmiedeberg's Archives of Pharmacology, (1995) 351/3 (305-308).

ISSN: 0028-1298 CODEN: NSAPCC

CY Germany
 DT Journal; Article
 FS 016 Cancer
 025 Hematology
 029 Clinical Biochemistry
 030 Pharmacology
 037 Drug Literature Index
 LA English
 SL English
 AB Formyl peptides activate superoxide anion (O₂⁻) formation in human neutrophils and in HL-60 cells via pertussis toxin (PTX)-sensitive guanine nucleotide-binding proteins (G-proteins), and histamine (HA) mediates inhibition of O₂⁻ formation via H₂-receptors. We have studied the effects of lipophilic arpromidine-derived guanidines, which are potent, full H₂-receptor agonists in the guinea pig atrium, on O₂⁻ formation and on activation of O-proteins in HL-60 membranes and on purified G-proteins. We have also studied the effects of a HA trifluoromethyl-toluidide derivative (HTMT), a cationic-amphiphilic HA derivative which activates O₂⁻ formation in HL-60 cells through a mechanism which is independent of known HA receptor subtypes, on G-protein activation. Guanidines, at concentrations, up to 30 μ M inhibited and, at concentrations above 30 μ M, enhanced formyl peptide-induced O₂⁻ formation in neutrophils. In HL-60 cells, guanidines per se activated O₂⁻ formation. The stimulatory effects of guanidines on O₂⁻ formation were not inhibited by H₁- or H₂-receptor antagonists. In HL-60 membranes, guanidines and HTMT, activated high-affinity GTPase in a PTX-sensitive manner. These substances also increased GTP hydrolysis effected by transducin and G(i)/G(o)-proteins. Our data suggest that lipophilic guanidines and HTMT may act as receptor-independent activators of PTX-sensitive G-proteins, resulting in stimulation of O₂⁻ formation.
 CT Medical Descriptors:
 *leukemia cell
 *neutrophil
 article
 cell strain hl 60
 concentration response
 controlled study
 drug mechanism
 drug synthesis
 human
 human cell
 hydrolysis
 lipophilicity
 Drug Descriptors:
 *histamine h2 receptor
 *arpromidine: PD, pharmacology
 *guanidine derivative: DV, drug development
 *guanidine derivative: PD, pharmacology
 *guanine nucleotide binding protein: EC, endogenous compound
 *guanosine triphosphate
 *histamine agonist: PD, pharmacology
 1 [3 (3,4 dichlorophenyl) 3 (2 pyridyl)propyl] 3 [3 (1h imidazol 4 yl)propyl]guanidine: DV, drug development
 1 [3 (3,4 dichlorophenyl) 3 (2 pyridyl)propyl] 3 [3 (1h imidazol 4 yl)propyl]guanidine: PD, pharmacology
 1 [3 (3,4 dichlorophenyl) 3 phenylpropyl] 3 [3 (1h imidazol 4 yl)propyl]guanidine: DV, drug development
 1 [3 (3,4 dichlorophenyl) 3 phenylpropyl] 3 [3 (1h imidazol 4 yl)propyl]guanidine: PD, pharmacology
 6 [2 (4 imidazolyl)ethylamino] n (4 trifluoromethylphenyl)heptanamide: DV, drug development
 6 [2 (4 imidazolyl)ethylamino] n (4 trifluoromethylphenyl)heptanamide: PD, pharmacology
 amphophile: PD, pharmacology
 bu e 64
 bu e 82
 cation: PD, pharmacology
 cimetidine: PD, pharmacology
 diphenhydramine: PD, pharmacology
 formylmethionylleucylphenylalanine: PD, pharmacology
 guanosine triphosphatase: EC, endogenous compound
 histamine derivative: DV, drug development
 histamine derivative: PD, pharmacology
 histamine h1 receptor antagonist: PD, pharmacology
 histamine h2 receptor agonist: PD, pharmacology

histamine h2 receptor antagonist: PD, pharmacology
 inhibitory guanine nucleotide binding protein
 pertussis toxin: TO, drug toxicity
 superoxide: EC, endogenous compound
 transducin

unclassified drug

RN (arpromidine) 106669-71-0; (guanosine triphosphate) 86-01-1; (cimetidine) 51481-61-9, 70059-30-2; (diphenhydramine) 147-24-0, 58-73-1; (guanosine triphosphatase) 9059-32-9; (pertussis toxin) 70323-44-3; (superoxide) 11062-77-4; (transducin) 94699-82-8
 CN Bu e 64; Bu e 82
 CO Cookson (United Kingdom)

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AN 95081931 EMBASE

DN 1995081931

TI Structural and conformational requirements for human calcitonin activity: Design, synthesis, and study of lactam-bridged analogues.

AU Kapurniotu A.; Taylor J.W.

CS Department of Chemistry, Rutgers University, P.O. Box 939, Piscataway, NJ 08855-0939, United States

SO Journal of Medicinal Chemistry, (1995) 38/5 (836-847).

ISSN: 0022-2623 CODEN: JMCMAR

CY United States

DT Journal; Article

FS 003 Endocrinology

030 Pharmacology

037 Drug Literature Index

LA English

SL English

AB The conformational and pharmacological effects of the introduction of conformational constraints in the form of i-(i + 4) lactam-bridges in the potential amphiphilic .alpha.-helical region (8-21) of human calcitonin (hCT) were studied. The following three cyclic hCT analogues were synthesized: cyclo[17,21-[Lys17,Asp21]hCT (1), cyclo[17,21-[Asp17,Lys21]hCT (2) and cyclo[10,14-[Lys10,Asp14]hCT (3). For their syntheses, solid-phase methodology was used in combination with either direct side chain to side chain cyclization on the solid support or a segment-condensation strategy. Circular dichroism studies in aqueous buffer, pH 7.0, indicated that the conformational effects were different for each lactam bridge introduced. Significant induction of .alpha.-helical structure was observed only for peptide 3. In contrast, peptide 1 and hCT had similar CD spectra, indicative of mixed disordered and .beta.-sheet conformations, and peptide 2 had a weaker spectrum consistent with the formation of a more ordered but nonhelical structure. In rat brain receptor binding assays, peptide 2 showed a nearly 80-fold higher potency than hCT or peptides 1 and 3. All three analogues stimulated adenylyl cyclase in the rat kidney membrane at 5-fold lower concentrations than hCT and with similar maximal effects. In vivo hypocalcemic assays, performed in mice by analysis of serum calcium levels 1 h after sc injection, indicated that peptide 2 had similar maximal effects to hCT and was 10-20 times more potent than hCT at doses giving half-maximal effects. In contrast, peptides 1 and 3 were not significantly more potent than hCT. Our findings indicate compatibility of all three lactam bridges and, most probably, also the amphiphilic .alpha.-helix, with the pharmacological activities of hCT. However, the properties of peptide 2 also suggest that another conformation, possibly a type I .beta.-turn involving residues 17-20, may play an important role. A multistep mechanism of receptor recognition by hCT that might account for these results is discussed.

CT Medical Descriptors:

*cyclization
 *hypocalcemia
 amino acid substitution
 animal experiment
 animal tissue
 article
 basolateral membrane
 brain membrane
 calcium blood level
 circular dichroism
 controlled study
 drug conformation
 drug design
 drug effect

drug potency
 drug receptor binding
 drug synthesis
 female
 male
 mouse
 nonhuman
 rat
 structure activity relation
 subcutaneous drug administration
 Drug Descriptors:

*calcitonin receptor
 brain receptor

*calcitonin: AN, drug analysis
 *calcitonin: DV, drug development
 *calcitonin: PD, pharmacology
 *calcitonin derivative: DV, drug development
 *calcitonin derivative: PD, pharmacology
 *calcitonin derivative: AN, drug analysis
 *lactam

adenylate cyclase: EC, endogenous compound

aspartic acid

calcitonin[10 lysine,14 aspartic acid lactam]: PD, pharmacology
 calcitonin[10 lysine,14 aspartic acid lactam]: DV, drug development
 calcitonin[10 lysine,14 aspartic acid lactam]: AN, drug analysis
 calcitonin[17 aspartic acid,21 lysine lactam]: AN, drug analysis
 calcitonin[17 aspartic acid,21 lysine lactam]: PD, pharmacology
 calcitonin[17 aspartic acid,21 lysine lactam]: DV, drug development
 calcitonin[17 lysine,21 aspartic acid lactam]: AN, drug analysis
 calcitonin[17 lysine,21 aspartic acid lactam]: PD, pharmacology
 calcitonin[17 lysine,21 aspartic acid lactam]: DV, drug development
 calcium ion: EC, endogenous compound

lysine

salcatonin

unclassified drug

RN (calcitonin) 12321-44-7, 21215-62-3, 9007-12-9; (adenylate cyclase)
 9012-42-4; (aspartic acid) 56-84-8, 6899-03-2; (calcium ion) 14127-61-8;
 (lysine) 56-87-1, 6899-06-5, 70-54-2; (salcatonin) 47931-85-1
 CO Bachem (United States); Aldrich; Fisher; Fluka; Sigma; Amersham

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 on STN

AN 94366690 EMBASE

DN 1994366690

TI Cholesterol homeostasis. Modulation by amphiphiles.

AU Lange Y.; Steck T.L.

CS Dept. of Pathology, Rush-Presbyterian-SLMC, 1653 W. Congress
 Pkwy., Chicago, IL 60612, United States

SO Journal of Biological Chemistry, (1994) 269/47 (29371-29374).
 ISSN: 0021-9258 CODEN: JBCHA3

CY United States

DT Journal; Article

FS 029 Clinical Biochemistry

030 Pharmacology

037 Drug Literature Index

LA English

SL English

AB Diverse amphiphiles act on cellular cholesterol metabolism as if
 signaling regulatory sites. One class (oxysterols) mimics the homeostatic
 effects of excess cell cholesterol, inhibiting cholesterol biosynthesis
 and stimulating plasma membrane cholesterol esterification. A second class
 of amphiphiles has effects precisely opposite to the oxysterols,
 i.e. they immediately inhibit plasma membrane cholesterol esterification
 and progressively induce 3- hydroxy-3-methylglutaryl-coenzyme A reductase
 activity and cholesterol biosynthesis. This second class of agents
 includes steroids, hydrophobic amines, phenothiazines, ionophores,
 colchicine, cytochalasins, and lysophosphatides, most of which interact
 with P-glycoproteins. These data support a general hypothesis describing
 cellular cholesterol homeostasis. (a) Proteins regulating sterol
 metabolism are embedded in intracellular membranes where their activities
 are governed by the local level of cholesterol. (b) Excess plasma membrane
 and lysosomal cholesterol circulates through those intracellular membranes
 and sets the homeostatic activities therein. (c) The two classes of agents
 mentioned above affect cholesterol homeostasis by increasing or
 decreasing, respectively, the ambient level of cholesterol at the sites of
 regulation.

CT Medical Descriptors:
 *cholesterol esterification
 *cholesterol synthesis
 animal cell
 article
 cholesterol metabolism
 controlled study
 drug antagonism
 enzyme activity
 fibroblast
 hepatoma cell
 human
 human cell
 nonhuman
 priority journal
 rat
 Drug Descriptors:
 *low density lipoprotein receptor
 *amphophile: IT, drug interaction
 *amphophile: PD, pharmacology
 *amphophile: CB, drug combination
 *cholesterol
 *glycoprotein p: EC, endogenous compound
 *hydroxymethylglutaryl coenzyme a reductase: EC, endogenous compound
 *hydroxysterol: IT, drug interaction
 *hydroxysterol: PD, pharmacology
 *sterol derivative: PD, pharmacology
 *sterol derivative: IT, drug interaction
 *sterol derivative: CB, drug combination
 25 hydroxycholesterol: CB, drug combination
 25 hydroxycholesterol: PD, pharmacology
 25 hydroxycholesterol: IT, drug interaction
 3beta (2 diethylaminoethoxy)androst 5 en 17 one: PD, pharmacology
 3beta (2 diethylaminoethoxy)androst 5 en 17 one: IT, drug interaction
 3beta (2 diethylaminoethoxy)androst 5 en 17 one: CB, drug combination
 chloroquine: IT, drug interaction
 chloroquine: CB, drug combination
 chloroquine: PD, pharmacology
 colchicine: PD, pharmacology
 cytochalasin a: CB, drug combination
 cytochalasin a: PD, pharmacology
 cytochalasin a: IT, drug interaction
 cytochalasin b: CB, drug combination
 cytochalasin b: IT, drug interaction
 cytochalasin b: PD, pharmacology
 cytochalasin d: CB, drug combination
 cytochalasin d: PD, pharmacology
 cytochalasin d: IT, drug interaction
 estradiol: PD, pharmacology
 fluoride sodium
 hydroxysterol derivative: CB, drug combination
 imipramine: PD, pharmacology
 low density lipoprotein: EC, endogenous compound
 lysophosphatidylcholine: PD, pharmacology
 monensin: PD, pharmacology
 monensin: IT, drug interaction
 monensin: CB, drug combination
 nigericin: PD, pharmacology
 nigericin: IT, drug interaction
 nigericin: CB, drug combination
 oleic acid
 oxysterol derivative: IT, drug interaction
 oxysterol derivative: CB, drug combination
 oxysterol derivative: PD, pharmacology
 pregnenolone: PD, pharmacology
 progesterone: IT, drug interaction
 progesterone: PD, pharmacology
 progesterone: CB, drug combination
 testosterone: PD, pharmacology
 trifluoperazine: PD, pharmacology
 unclassified drug
 RN (cholesterol) 57-88-5; (hydroxymethylglutaryl coenzyme a reductase)
 37250-24-1; (25 hydroxycholesterol) 2140-46-7; (3beta (2
 diethylaminoethoxy)androst 5 en 17 one) 3039-71-2; (chloroquine) 132-73-0,
 3545-67-3, 50-63-5, 54-05-7; (colchicine) 64-86-8; (cytochalasin a)
 14110-64-6; (cytochalasin b) 14930-96-2; (cytochalasin d) 22144-77-0;

(estradiol) 50-28-2; (fluoride sodium) 51668-54-3, 7681-49-4, 79933-27-0;
 (imipramine) 113-52-0, 50-49-7; (lysophosphatidylcholine) 93794-93-5;
 (monensin) 17090-79-8, 22373-78-0; (nigericin) 28380-24-7; (oleic acid)
 112-80-1, 115-06-0; (pregnenolone) 145-13-1; (progesterone) 57-83-0;
 (testosterone) 58-22-0; (trifluoperazine) 117-89-5, 440-17-5

CN U 18666 a

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AN 94146405 EMBASE

DN 1994146405

TI The H1 receptor agonist 2-(3-chlorophenyl)histamine activates G(i)
 proteins in HL-60 cells through a mechanism that is independent of known
 histamine receptor subtypes.

AU Seifert R.; Hagelucken A.; Hoer A.; Hoer D.; Grunbaum L.; Offermanns S.;
 Schwaner I.; Zingel V.; Schunack W.; Schultz G.

CS Institut fur Pharmakologia, Freie Universitat Berlin, Thielallee
 69-73, D-14195 Berlin, Germany

SO Molecular Pharmacology, (1994) 45/4 (578-586).

ISSN: 0026-895X CODEN: MOPMA3

CY United States

DT Journal; Article

FS 030 Pharmacology

037 Drug Literature Index

LA English

SL English

AB In dibutyryl-cAMP-differentiated HL-60 cells, histamine H1 and formyl
 peptide receptors mediate increases in the cytosolic Ca²⁺ concentration
 ([Ca²⁺](i)) via pertussis toxin-sensitive G proteins of the G(i) family.
 We compared the effects of 2-(3-chlorophenyl)-histamine (CPH) [2-[2-(3-
 chlorophenyl)-1H-imidazol-4-yl] ethanamine], one of the most potent and
 selective H1 receptor agonists presently available, with those of
 histamine and N-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMLP) in
 these cells. CPH increased [Ca²⁺](i) through Ca²⁺ mobilization and Ca²⁺
 influx. Unlike histamine-induced rises in [Ca²⁺](i), those induced by CPH
 were not desensitized in a homologous manner, and there was no
 cross-desensitization between CPH and histamine. Like fMLP, CPH activated
 phospholipases C and D, tyrosine phosphorylation, superoxide anion
 formation, and azurophilic granule release. The effects of CPH on
 [Ca²⁺](i), phospholipase D, and superoxide anion formation were inhibited
 by pertussis toxin. CPH and fMLP stimulated high affinity GTP hydrolysis
 by G(i) proteins in HL-60 membranes. They also enhanced binding of
 guanosine-5'-O-(3-thio)triphosphate and GTP azidoanilide to, and cholera
 toxin-catalyzed ADP-ribosylation of G(i) protein .alpha. subunits.
 Histamine receptor antagonists did not inhibit the stimulatory effects of
 CPH, and CPH did not reduce fMLP binding in HL-60 membranes. Our data
 suggest that CPH activates G(i) proteins in HL-60 cells through a receptor
 agonist-like mechanism that is, however, independent of known histamine
 receptor subtypes and formyl peptide receptors. CPH may be an agonist at
 an as yet unknown histamine receptor subtype or by analogy with other
 cationic- amphiphilic substances, may activate G proteins
 directly. Future studies will have to take into consideration the fact
 that CPH, in addition to activating H1 receptors, may show other, most
 unexpected, stimulatory effects on G protein mediated signal transduction
 processes.

CT Medical Descriptors:

article

calcium cell level

calcium mobilization

calcium transport

cell strain hl 60

controlled study

drug activity

drug mechanism

enzyme activation

human

human cell

Drug Descriptors:

*histamine h1 receptor
 receptor subtype

*histamine h1 receptor agonist: CM, drug comparison

*histamine h1 receptor agonist: PD, pharmacology

2 (3 chlorophenyl)histamine: CM, drug comparison

2 (3 chlorophenyl)histamine: PD, pharmacology

calcium ion: EC, endogenous compound

formylmethionylleucylphenylalanine: CM, drug comparison

guanosine 5' o (3 thiotriphosphate)
 histamine: CM, drug comparison
 inhibitory guanine nucleotide binding protein
 pertussis toxin
 phospholipase c
 phospholipase d
 unclassified drug

RN (calcium ion) 14127-61-8; (guanosine 5' o (3 thiotriphosphate))
 37589-80-3; (histamine) 51-45-6, 56-92-8, 93443-21-1; (pertussis toxin)
 70323-44-3; (phospholipase c) 9001-86-9; (phospholipase d) 9001-87-0

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AN 93039519 EMBASE

DN 1993039519

TI Differential insertion of insulin receptor complexes into Triton X-114
 bilayer membranes. Evidence for a differential accessibility of the
 membrane-exposed receptor domain.

AU Florke R.-R.; Klein H.W.; Reinauer H.

CS Diabetes-Forschungsinstitut, Auf'm Hennekamp 65, W-4000 Dusseldorf, Germany

SO European Journal of Biochemistry, (1993) 211/1-2 (241-247).

ISSN: 0014-2956 CODEN: EJBCAI

CY Germany

DT Journal; Article

FS 029 Clinical Biochemistry

LA English

SL English

AB In the present study, the Triton X-114 phase-separation system has been
 used to characterize molecular properties of the membrane-exposed domain
 of an integral-membrane hormone receptor. This approach provides novel
 details of the structure/function relationship of insulin receptors. Upon
 raising the temperature of a micellar Triton X-114 solution above the
 cloud-point, a detergent enriched phase pellets and coprecipitates 95% of
 the purified insulin-free (.alpha..beta.)₂ receptors. In contrast, 83% of
 the hormone bound (.alpha..beta.)₂ receptor complexes prefer the
 detergent-depleted phase, exhibiting prominent properties of
 non-membraneous proteins. Kinetic studies show that, following insulin
 binding, the amphiphilicity of the receptor complexes is
 immediately altered. Only monodisperse (.alpha..beta.)₂ complexes were
 detected when receptor/insulin complexes of the detergent-depleted phase
 were analyzed by detergent-free sucrose density centrifugation in the
 presence of 10 nM insulin. These results can be explained in the light of
 the lipid-bilayer-like organization of the precipitating Triton X-114;
 hormone-induced intramolecular alterations of (.alpha..beta.)₂ receptors
 appear to fundamentally restrict access to the membrane-exposed receptor
 domain. Basically, different molecular properties are found for
 .alpha..beta. receptors. Only 67% of the insulin-free .alpha..beta.
 receptors coprecipitate with the Triton-X-114-enriched phase; following
 insulin binding the coprecipitation is only decreased to 42%. In contrast
 to (.alpha..beta.)₂ receptors, formation of noncovalently aggregated
 receptor complexes, which are detected by sucrose density centrifugation,
 could account for the exclusion of .alpha..beta. receptor species from
 Triton X-114 membranes.

CT Medical Descriptors:

*receptor binding

*structure activity relation

article

human

human tissue

priority journal

Drug Descriptors:

*insulin receptor

*insulin

triton x 114

unclassified drug

RN (insulin) 9004-10-8; (triton x 114) 9036-19-5

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AN 87182320 EMBASE

DN 1987182320

TI Synthesis of two glucagon antagonists: Receptor binding, adenylate
 cyclase, and effects on blood plasma glucose levels.

AU Gysin B.; Johnson D.G.; Trivedi D.; Hruby V.J.

CS Department of Chemistry, University of Arizona, Tucson, AZ 85721, United
 States

SO Journal of Medicinal Chemistry, (1987) 30/8.(1409-1415).

CODEN: JMCMAR

CY United States

DT Journal

FS 037 Drug Literature Index

029 Clinical Biochemistry

030 Pharmacology

LA English

AB In diabetes mellitus, hyperglycemia is often associated with elevated levels of glucagon in the blood. This suggests that glucagon (1) is a contributing factor in the metabolic abnormalities of diabetes mellitus. A glucagon-receptor antagonist would provide direct evidence for glucagon's role in diabetes mellitus. On the basis of careful consideration of conformational, amphiphilic, and structural factors, we have synthesized two new glucagon analogues with antagonist biological activities by using solid-phase methodology. These two new analogues, [Asp3,D-Phe4,Ser5,Lys17,18,Glu21]glucagon (2) and [D-Phe4,Tyr5,3,5-I2-Tyr10,Arg12,Lys17,18,Glu21]glucagon (3), had IC50 values 5.4% and 50% those of glucagon, respectively, and showed no measurable adenylate cyclase activity. When tested in normal rats, 2 lowered plasma glucose levels and suppressed glucagon-mediated hyperglycemia 105 \pm 8%, back to basal levels. Analogue 3, which lowered the basal adenylate cyclase activity in rat liver plasma membranes, increased plasma glucose levels at very high concentration in vivo and inhibited glucagon-mediated hyperglycemia in normal rats by 50%. However, neither of the new glucagon antagonists lowered the plasma glucose levels of diabetic animals. The data would suggest these new glucagon-receptor antagonists may have two actions: (a) in normal rats they can act as standard glucagon-receptor inhibitors of glucagon-mediated glycogenolysis; (b) in diabetic rats, however, because of the low levels of glycogen in the liver, the antagonists apparently have little or no antagonist effect or enhancement on glucagon-mediated glucose production.

CT Medical Descriptors:

*diabetes mellitus

*dose response

*drug antagonism

*drug comparison

*drug receptor binding

*drug screening

*drug synthesis

*glucagon antagonist

*glucose blood level

rat

endocrine system

pharmacokinetics

nonhuman

etiology

blood and hemopoietic system

normal value

therapy

liver

animal experiment

animal cell

animal model

Drug Descriptors:

*adenylate cyclase

*cyclic amp

*glucagon derivative

*glucagon receptor

streptozocin

*glucagon[3 aspartic acid 4 dextro phenylalanine 5 serine 17,18 lysine 21 glutamic acid]

*glucagon[4 dextro phenylalanine 5 tyrosine 10 (3,5 diiodotyrosine) 12 arginine 17,18 lysine 21 glutamic acid]

glucagon

glucagon i 125

new drug

radioisotope

unclassified drug

RN (adenylate cyclase) 9012-42-4; (cyclic amp) 60-92-4; (streptozocin)

18883-66-4; (glucagon) 11140-85-5, 62340-29-8, 9007-92-5

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AN 87179086 EMBASE

DN 1987179086

TI Interactions of beta adrenergic antagonists with isolated rat alveolar type II pneumocytes. II. Receptor-independent accumulation of beta adrenergic antagonists and other cationic amphiphilic drugs in lamellar bodies.

AU Fabisiak J.P.; Vesell E.S.; Rannels D.E.

CS Department of Pharmacology, College of Medicine, The Pennsylvania State University, The Milton S. Hershey Medical Center, Hershey, PA 17033, United States

SO Journal of Pharmacology and Experimental Therapeutics, (1987) 241/2 (728-735).

CODEN: JPETAB

CY United States

DT Journal

FS 037 Drug Literature Index
030 Pharmacology

LA English

CT Medical Descriptors:
*drug accumulation
*drug binding
*drug efficacy
*drug interaction
*lamellar body
*lymphoma cell
cell culture
lung alveolus cell
rat
priority journal
pharmacokinetics
respiratory system
in vitro study
nonhuman
animal cell
Drug Descriptors:
*beta adrenergic receptor
*beta adrenergic receptor blocking agent
*(9 aminoacridinyl)propranolol
*chloroquine
*chlorpromazine
*cyanopindolol i 125
*indometacin
*iodopindolol i 125
*phentolamine
*phenytoin
*quinidine
*thiopental
radioisotope
unclassified drug

RN ((9 aminoacridinyl)propranolol) 60566-40-7; (chloroquine) 132-73-0, 3545-67-3, 50-63-5, 54-05-7; (chlorpromazine) 50-53-3, 69-09-0; (cyanopindolol i 125) 81447-77-0; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (iodopindolol i 125) 76875-01-9; (phentolamine) 50-60-2, 73-05-2; (phenytoin) 57-41-0, 630-93-3; (quinidine) 56-54-2; (thiopental) 71-73-8, 76-75-5

CO Polyscience (United States); Sigma (United States)

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AN 1998275834 EMBASE

TI A system for the brain-enhanced delivery of estradiol: An assessment of its potential for the treatment of Alzheimer's disease and stroke.

AU Simpkins J.W.; Rabbani O.; Shi J.; Panickar K.S.; Green P.S.; Day A.L.

CS Dr. J.W. Simpkins, College of Pharmacy, University of Florida, Gainesville, FL 32610, United States

SO Pharmazie, (1998) 53/8 (505-511).

Refs: 88

ISSN: 0031-7144 CODEN: PHARAT

CY Germany

DT Journal; General Review

FS 008 Neurology and Neurosurgery
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index

LA English

CT Medical Descriptors:
 *alzheimer disease
 *stroke
 *brain
 *drug delivery system
 cholinergic nerve cell
 lipophilicity
 blood brain barrier
 hydrophilicity
 lipid solubility
 hydrolysis
 oxidation reduction reaction
 enzyme activity
 neuroprotection
 membrane depolarization
 calcium homeostasis
 human
 nonhuman
 review
 Drug Descriptors:
 *estradiol: AN, drug analysis
 *estradiol: PK, pharmacokinetics
 *estradiol: PD, pharmacology
 *dihydropyridine
 *pyridinium derivative
 *3 hydroxy 17beta [[[(1 methyl 1,4 dihydropyridine 3 yl)carbonyl]oxy]estra
 1,3,5 (10) triene: AN, drug analysis
 *1 methyl 3 [[[(3 hydroxyestra 1,3,5 (10) triene 17beta
 yl)oxy]carbonyl]pyridinium iodide: AN, drug analysis
 thromboxane: EC, endogenous compound
 lipid: EC, endogenous compound
 glucose: EC, endogenous compound
 oxygen: EC, endogenous compound
 excitatory amino acid: TO, drug toxicity
 choline acetyltransferase: EC, endogenous compound
 choline: EC, endogenous compound
 calcium: EC, endogenous compound
 cyclic amp responsive element binding protein: EC, endogenous compound
 messenger rna: EC, endogenous compound
 neurotrophin receptor: EC, endogenous compound
 neurotrophin: EC, endogenous compound
 mitogen activated protein kinase: EC, endogenous compound
 nerve growth factor: EC, endogenous compound
 amyloid beta protein: TO, drug toxicity
 glutamic acid: TO, drug toxicity
 buthionine sulfoximine: TO, drug toxicity
 hydrogen peroxide: TO, drug toxicity
 glucose transporter: EC, endogenous compound
 diethylstilbestrol
 neurotransmitter: EC, endogenous compound
 unclassified drug

RN (estradiol) 50-28-2; (dihydropyridine) 27790-75-6; (thromboxane)
 66719-58-2; (lipid) 66455-18-3; (glucose) 50-99-7, 84778-64-3; (oxygen)
 7782-44-7; (choline acetyltransferase) 9012-78-6; (choline) 123-41-1,
 13232-47-8, 1927-06-6, 4858-96-2, 62-49-7, 67-48-1; (calcium) 7440-70-2;
 (cyclic amp responsive element binding protein) 130428-87-4, 130939-96-7;
 (mitogen activated protein kinase) 142243-02-5; (nerve growth factor)
 9061-61-4; (amyloid beta protein) 109770-29-8; (glutamic acid) 11070-68-1,
 138-15-8, 56-86-0, 6899-05-4; (buthionine sulfoximine) 5072-26-4;
 (hydrogen peroxide) 7722-84-1; (diethylstilbestrol) 30498-85-2, 56-53-1

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AN 97275017 EMBASE
 DN 1997275017

TI Use of conformationally restricted benzamidines as arginine surrogates in
 the design of platelet GPIIb-IIIa receptor antagonists.

AU Sall D.J.; Arfsten A.E.; Bastian J.A.; Denney M.L.; Harms C.S.; McCowan
 J.R.; Morin J.M. Jr.; Rose J.W.; Scarborough R.M.; Smyth M.S.; Um S.L.;
 Utterback B.G.; Vasileff R.T.; Wikel J.H.; Wyss V.L.; Jakubowski J.A.

CS D.J. Sall, Lilly Research Laboratories, Eli Lilly and Company,
 Indianapolis, IN 46285, United States

SO Journal of Medicinal Chemistry, (1997) 40/18 (2843-2857).
 Refs: 37
 ISSN: 0022-2623 CODEN: JMCMAR

CY United States

DT Journal; Article
 FS 025 Hematology
 030 Pharmacology
 037 Drug Literature Index
 LA English
 SL English
 AB The use of 5,6-bicyclic amidines as arginine surrogates in the design of a novel class of potent platelet glycoprotein IIb-IIIa receptor (GPIIb-IIIa) antagonists is described. The additional conformational restriction offered by the bicyclic nucleus results in 20-400-fold increases in potency compared to the freely flexible, acyclic benzamidine counterpart. The design, synthesis, structure-activity relationships (SAR), and in vitro activity of this novel class of GPIIb-IIIa antagonists are presented.
 CT Medical Descriptors:
 *drug conformation
 *drug design
 *thrombocyte aggregation inhibition
 article
 drug potency
 drug receptor binding
 drug synthesis
 enzyme linked immunosorbent assay
 hydrogen bond
 hydrophilicity
 lipophilicity
 structure activity relation
 thrombocyte rich plasma
 Drug Descriptors:
 *arginine derivative
 *benzamidine derivative: AN, drug analysis
 *benzamidine derivative: PD, pharmacology
 *benzamidine derivative: DV, drug development
 *bicyclo compound
 *fibrinogen receptor antagonist: PD, pharmacology
 *fibrinogen receptor antagonist: DV, drug development
 *fibrinogen receptor antagonist: AN, drug analysis
 4 nitrophenyl phosphate
 adenosine diphosphate
 alkaline phosphatase
 arginylglycylaspartic acid
 avidin
 benzofuran derivative
 bovine serum albumin
 fibrinogen
 human serum albumin
 vitronectin receptor
 RN (4 nitrophenyl phosphate) 330-13-2; (adenosine diphosphate) 20398-34-9, 58-64-0; (alkaline phosphatase) 9001-78-9; (arginylglycylaspartic acid) 99896-85-2; (fibrinogen) 9001-32-5; (human serum albumin) 9048-49-1
 CO Sigma (United States); Biorad (United States); Aldrich (United States)

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